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Patient Name: 윤정호
Gender: M
Sample ID: N25-38

Primary Tumor Site: colon
Collection Date: 2025.05.13

Sample Cancer Type: Colorectal Cancer

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Relevant Colorectal Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK2	None detected
ERBB2	None detected	NTRK3	None detected
KRAS	***KRAS p.(G12V) c.35G>T***	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***7.58 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KRAS p.(G12V) c.35G>T* KRAS proto-oncogene, GTPase Allele Frequency: 38.14% Locus: chr12:25398284 Transcript: NM_033360.4	bevacizumab + chemotherapy [I]	None*	21
IIC	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	2
IIC	*Microsatellite stable*	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.

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: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC p.(R216) c.646C>T, CDKN2C deletion, CUL4A p.(R687Sfs*5) c.2061_2062delAG, FBXW7 p.(Q612Vfs*31) c.1834_1835delCA, FBXW7 p.(R367*) c.1099C>T, MUTYH deletion, RAD54L deletion, SDHB deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, JAK1 deletion, FUBP1 deletion, DPYD deletion, NOTCH2 deletion, CDH10 p.(R638*) c.1912C>T, HLA-B deletion, HDAC9 p.(A625Qfs*19) c.1872delA, NQO1 p.(P187S) c.559C>T, CANT1::ETV4 fusion, RUNX1 deletion, CYP2D6 c.506-1G>A, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FBXW7	p.(Q612Vfs*31)	c.1834_1835delCA	.	chr4:153245355	40.92%	NM_033632.3	frameshift Deletion
FBXW7	p.(R367*)	c.1099C>T	COSM22964	chr4:153251907	39.40%	NM_033632.3	nonsense
CDH10	p.(R638*)	c.1912C>T	.	chr5:24488227	37.37%	NM_006727.5	nonsense
APC	p.(R216*)	c.646C>T	COSM98420	chr5:112128143	78.08%	NM_000038.6	nonsense
HDAC9	p.(A625Qfs*19)	c.1872delA	.	chr7:18767342	5.14%	NM_178425.3	frameshift Deletion
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	38.14%	NM_033360.4	missense
CUL4A	p.(R687Sfs*5)	c.2061_2062delAG	.	chr13:113914944	27.93%	NM_001008895.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.25%	NM_000903.3	missense
CYP2D6	p.(?)	c.506-1G>A	COSM5019461	chr22:42524947	50.84%	NM_000106.6	unknown
HLA-A	p.(L192R)	c.575T>G	.	chr6:29911276	86.22%	NM_001242758.1	missense
HLA-C	p.([V328=;T329A;A330V;M331V])	c.984_991delCACCGCTAinsGGCTGTTG	.	chr6:31237767	100.00%	NM_001243042.1	synonymous, missense, missense, missense
KMT2A	p.(A3077V)	c.9230C>T	.	chr11:118375837	40.15%	NM_001197104.2	missense
TSHR	p.(A471T)	c.1411G>A	.	chr14:81609813	40.35%	NM_000369.5	missense
ZNF682	p.(R473Sfs*11)	c.1415_1416delAG	.	chr19:20116894	50.33%	NM_033196.3	frameshift Deletion

Gene Fusions

Genes	Variant ID	Locus
CANT1::ETV4	CANT1-ETV4.C2E5.redesign.1	chr17:77001454 - chr17:41613847

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
TNFRSF14	chr1:2488070	1.04	0.62
ERRFI1	chr1:8073246	1.15	0.67
ENO1	chr1:8921399	1.08	0.64
PGD	chr1:10459132	0.94	0.58

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
SPEN	chr1:16174516	1.03	0.62
EPHA2	chr1:16451707	1.13	0.65
SDHB	chr1:17345303	1.06	0.63
ARID1A	chr1:27022875	1.03	0.62
MUTYH	chr1:45794962	1.11	0.65
RAD54L	chr1:46714017	1	0.62
CDKN2C	chr1:51434849	0.89	0.56
JAK1	chr1:65300225	1	0.61
FUBP1	chr1:78414385	0.96	0.59
DPYD	chr1:97544504	0.94	0.58
NOTCH2	chr1:120457903	0.97	0.59
HLA-B	chr6:31322252	1	0.61
RUNX1	chr21:36164357	1.08	0.63
MYCL	chr1:40362966	0.9	0.56
MPL	chr1:43803495	1.15	0.67
MAGOH	chr1:53692690	1.01	0.61
NRAS	chr1:115251152	1.01	0.61
U2AF1L5	chr21:44513260	1	0.6

Biomarker Descriptions

DPYD deletion

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DPYD.

Biomarker Descriptions (continued)

CDH10 p.(R638*) c.1912C>T

cadherin 10

Background: The CDH10 gene encodes cadherin 10, a type II classical cadherin and member of the cadherin superfamily[1]. Cadherins are important in calcium-dependent cell-cell adhesion, and are known to mediate cell recognition, cell movement, and maintain structural and functional cell and tissue polarity[6]. CDH10 is classified as an atypical type II cadherin due to its lack of a histidine-alanine-valine (HAV) cell adhesion recognition motif, a hallmark characteristic to type I cadherins[1,6]. Abnormal expression of cadherins results in increased tumor cell invasion, which precedes metastasis of tumors[7,8].

Alterations and prevalence: Somatic mutations of CDH10 are observed in 20% of lung squamous cell carcinoma, 16% of lung adenocarcinoma, 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 8% of stomach adenocarcinoma, and colorectal adenocarcinoma, 6% of head and neck squamous cell carcinoma, 4% of bladder urothelial carcinoma and esophageal adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and sarcoma[4,5]. Amplification of CDH10 is observed in 10% of lung squamous cell carcinoma, 7% of lung adenocarcinoma and esophageal adenocarcinoma, 6% of bladder urothelial carcinoma, 5% of ovarian serous cystadenocarcinoma and cervical squamous cell carcinoma, 4% of sarcoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% uterine corpus endometrial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CDH10 aberrations.

CUL4A p.(R687Sfs*5) c.2061_2062delAG

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[1,9]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[10]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[10,11]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[9]. CUL4A is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[11]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[10,11].

Alterations and prevalence: Somatic mutations in CUL4A are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma[4,5]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[4,5]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[4,5]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for CUL4A aberrations.

CYP2D6 c.506-1G>A

cytochrome P450 family 2 subfamily D member 6

Background: The CYP2D6 gene encodes cytochrome P450 family 2 subfamily D member 6, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,12]. CYP2D6 is a key enzyme involved in the biotransformation of the prodrug tamoxifen to its active metabolites, endoxifen and 4-hydroxytamoxifen[13,14]. The CYP2D6 gene is highly polymorphic, and inherited CYP2D6 polymorphisms in individuals may result in absent, reduced, normal, or high CYP2D6 enzyme activity leading to poor, intermediate, normal, or ultrarapid metabolism of tamoxifen[13,14,15,16]. CYP2D6 genotype may impact response to tamoxifen treatment and clinical outcomes[15].

Alterations and prevalence: Somatic mutations in CYP2D6 are observed in 4% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma, skin cutaneous melanoma, and kidney chromophobe[4,5]. Biallelic loss of CYP2D6 is observed in 2% of ovarian serous cystadenocarcinoma[4,5]. Amplification of CYP2D6 is observed in 4% of skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CYP2D6.

Biomarker Descriptions (continued)

MUTYH deletion

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein[1]. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA[17]. MUTYH functions by removing adenine residues that have been misincorporated opposite of 8-oxoG (7,8-dihydro-8-oxoguanine) and FapyG (2,6-diamino-4-hydroxy-5-formamidopyrimidine)[17]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[18,19].

Alterations and prevalence: Somatic mutations in MUTYH are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 2% of lung squamous cell carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma[4,5]. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma[4,5].

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

SDHB deletion

succinate dehydrogenase complex iron sulfur subunit B

Background: The SDHB gene encodes succinate dehydrogenase complex iron sulfur subunit B, a subunit of the succinate dehydrogenase (SDH) enzyme complex[1]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[20,21]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[20,21]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[22]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[20,21]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,23].

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma[4,5]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[24,25]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[25]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[24,25].

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

ARID1A deletion

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,26]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[26,27]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[27]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[27,28]. ARID1A binds to transcription

Biomarker Descriptions (continued)

factors and coactivator/corepressor complexes to alter transcription[26]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[26].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[28]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[26]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[4,5,27]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[29].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[30], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[31], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[32]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[33]. 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[34,35,36]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[37].

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[4,5]. Biallelic loss of HLA-B is observed in 5% of DLBCL[4,5].

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

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[38]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[38,39,40]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[38,41]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[42]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[43].

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[44] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[45], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FBXW7 p.(Q612Vfs*31) c.1834_1835delCA, FBXW7 p.(R367*) c.1099C>T

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[46]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations

Biomarker Descriptions (continued)

or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[46,47,48,49,50,51,52].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[4,5,53,54,55].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[56], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[53]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[52].

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[57]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[58,59]. 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[60]. 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[61]. 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)[61]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[62,63,64,65,66]. 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[59]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[58,59,63,67].

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[58,59,68,69]. 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[68,69].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[70] (2014) and nivolumab[71] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[70] 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[70]. Dostarlimab[72] (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[64,73]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[74] (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[64,75,76]. 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 patients[76]. 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].

APC p.(R216*) c.646C>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 differentiation[79]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[80,81]. 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[79,82]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[83].

Biomarker Descriptions (continued)

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[4,5,84]. 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[85,86].

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

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,87]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[87]. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/β-catenin[87,88,89]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[87,88,90]. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion[87,88].

Alterations and prevalence: Somatic mutations in ENO1 are observed in 3% uterine corpus endometrial carcinoma and kidney chromophobe, and 2% of diffuse large B-cell lymphoma, skin cutaneous melanoma, and cervical squamous cell carcinoma[4,5]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[4,5]. Biallelic loss of ENO1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma, and 2% of pheochromocytoma and paraganglioma, liver hepatocellular carcinoma, and diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for ENO1 aberrations.

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[91,92,93].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,94,95]. Mutations at A59, K117, and A146 have also been observed but are less frequent[5,96].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[97] (2021) and adagrasib[98] (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[99]. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[100], for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398[101] 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[102] 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[103], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001[104], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[105], 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[106] and panitumumab[107], 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)[96]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[108].

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[109]. All RUNX proteins share several conserved regions with similar functionality including

Biomarker Descriptions (continued)

a highly conserved N-terminal 'runt' domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[110]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[111,112]. RUNX1 is frequently mutated in various hematological malignancies[112]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[113,114]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[112].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[115]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 20-25% of childhood ALL[116,117]. This translocation is also observed in adult ALL at a lower frequency (2%)[117]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[118]. The RUNX1::RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[112,118]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[112]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,112,119,120].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[119,121]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6::RUNX1 in ALL, are associated with favorable risk[122,123]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[120,122,124].

CANT1::ETV4 fusion

ETS variant 4, calcium activated nucleotidase 1

Background: The ETV4 gene encodes the E twenty-six (ETS) variant 4 transcription factor. ETV1, ETV4, and ETV5 belong to the PEA3-subfamily of the ETS family of transcription factors that regulate cell cycle, differentiation, proliferation, and survival[125,126].

Alterations and prevalence: Recurrent chromosomal rearrangement leading to overexpression of the androgen-activated TMPRSS2::ETV4 gene fusion is an early event in prostate cancer development and is observed in 1-5% of cases[4,127,128].

Potential relevance: Currently, no therapies are approved for ETV4 aberrations. Translocation t(12;15)(p13;q25) resulting in ETV6::NTRK3 fusion is used as an ancillary diagnostic marker in infantile fibrosarcoma[129]. Fusion of EWSR1 to an ETS family member (including EWSR1::ETV4 fusion) is diagnostic of Ewing Sarcoma[130].

NOTCH2 deletion

notch 2

Background: The NOTCH2 gene encodes the notch receptor 2 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[131]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[132,133]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[134,135,136,137].

Alterations and prevalence: Somatic mutations observed in NOTCH2 are primarily missense or truncating and are found in about 11% of uterine cancer, 6% of melanoma and stomach cancer, as well as 3-5% diffuse large B-cell lymphoma (DLBCL), lung, colorectal, bladder, cervical, and head and neck cancers[4].

Potential relevance: Currently, no therapies are approved for NOTCH2 aberrations.

FUBP1 deletion

far upstream element binding protein 1

Background: The FUBP1 gene encodes the far upstream element binding protein 1, a DNA/RNA binding protein implicated in a variety of cellular functions[1,138]. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of

Biomarker Descriptions (continued)

transcription, translation, and splicing[138]. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis[138]. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation[138].

Alterations and prevalence: Somatic mutations in FUBP1 are observed in 9% of brain lower grade glioma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of colorectal adenocarcinoma[4,5]. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions[138]. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma[4,5]. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q[138].

Potential relevance: Currently, no therapies are approved for FUBP1 aberrations.

HDAC9 p.(A625Qfs*19) c.1872delA

histone deacetylase 9

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[1]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[139]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[139,140]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[139]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[139,141].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[142]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[143]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[144]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[145].

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP+ to NADPH[1,146]. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation[147,148]. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation[146,149].

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma[4,5]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5].

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

CDKN2C deletion

cyclin dependent kinase inhibitor 2C

Background: CDKN2C encodes the cyclin-dependent kinase inhibitor 2C protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2C, also known as p18/INK4C, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which includes CDKN2A (p16/INK4A), CDKN2B (p15/INK4B), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6,

Biomarker Descriptions (continued)

thereby preventing the phosphorylation of Rb[150,151,152]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[153].

Alterations and prevalence: Somatic mutations in CDKN2C are observed in 2% of uterine corpus endometrial carcinoma and glioblastoma. Biallelic deletion of CDKN2C is observed in 3% of glioblastoma and 2% of pheochromocytoma, paraganglioma, brain lower grade glioma, kidney chromophobe, and sarcoma[4,5]. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study[154,155,156].

Potential relevance: Currently, no therapies are approved for CDKN2C aberrations.

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[157,158,159]. As a transcriptional repressor, SPEN sequesters transcriptional activators and interacts with other repressors and chromatin remodeling complexes, such as histone deacetylases (HDACs) and the NuRD complex[157,159]. In ERα-positive breast cancers, SPEN binds ERα in a ligand-independent manner and negatively regulates the transcription of ERα targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival[160,161].

Alterations and prevalence: Somatic mutations in SPEN are observed in 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 10% of stomach adenocarcinoma, 7% of diffuse large B-cell lymphoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and lung adenocarcinoma, 4% of lung squamous cell carcinoma and ovarian serous cystadenocarcinoma, 3% of kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, glioblastoma multiforme, and acute myeloid leukemia, and 2% of pancreatic adenocarcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma[4,5]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,162]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[162,163]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[162,164]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[162,165,166,167,168]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[162,165,166,169,170].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ERRFI1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[4,5].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[171]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[171]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[171,172]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[171]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[172].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[173]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[174,175].

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)[1,176]. JAK1 is a member of the Janus kinase (JAK) family that includes JAK1, JAK2, JAK3, and TYK2[176]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[177]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[177,178,179]. Since JAK1 mediates interferon-γ regulated tumor surveillance, inactivation of JAK1 is believed to inhibit presentation of tumor antigens and contribute to immune evasion[179,180,181].

Alterations and prevalence: Activating missense mutations in JAK1 that result in constitutive signal transduction are observed in up to 20% of adult T-cell lymphoblastic leukemia[182,183,184]. The recurrent somatic mutation V658F observed in JAK1 is homologous to the V617F mutation in JAK2 known to be a driver mutation in myeloproliferative disease[183]. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers although two variants, S703I and S729C, were reported in hepatocellular carcinomas[185,186,187]. In addition, V658F and R724H were infrequently observed in diverse cancer types[4]. Truncating mutations in JAK1, as a result of dispersed or recurrent frameshift mutations, are common in solid cancers and particularly enriched in uterine cancers[4]. Recurrent truncating mutations in JAK1 were associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)[180,181].

Potential relevance: Currently, no therapies are approved for JAK1 aberrations. However, ruxolitinib[188] is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL[123]. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[189].

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.(G12V) c.35G>T

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

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

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.(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 1.2025]

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

cetuximab

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

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

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

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.(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:** 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.(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, 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.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	✖	✖	✖	●	✖
bevacizumab + FOLFIRI	✖	✖	✖	●	✖
bevacizumab + FOLFOX	✖	✖	✖	●	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	●	✖
bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)
fruquintinib, chemotherapy	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
afatinib, selumetinib	✖	✖	✖	✖	● (I/II)
anti-KRAS G12V mTCR, chemotherapy, aldesleukin	✖	✖	✖	✖	● (I/II)
IMM-1-104	✖	✖	✖	✖	● (I/II)
YL-15293	✖	✖	✖	✖	● (I/II)
AFNT-211	✖	✖	✖	✖	● (I)
HMPL-415	✖	✖	✖	✖	● (I)
IX-001	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✖	✖	✖	✖	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✖	✖	✖	✖	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✖	✖	✖	✖	● (I)
LY-4066434, cetuximab, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
NW-301V	✖	✖	✖	✖	● (I)
QTX-3544, cetuximab	✖	✖	✖	✖	● (I)
RMC-6236	✖	✖	✖	✖	● (I)

ARID1A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (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

Microsatellite stable

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✖	✖	✖	✖	● (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
LOH percentage	***13.06%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x3***
RAD54L	***CNV, CN:1.0***
RAD54L	***LOH, 1p34.1(46714017-46743978)x1***

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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