삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 성일영
Gender: M
Sample ID: N25-214

Primary Tumor Site: colon
Collection Date: 2025.08.22

Sample Cancer Type: Colon Cancer

Table of Contents	Page

Report Highlights
5 Relevant Biomarkers
22 Therapies Available
37 Clinical Trials

Relevant Colon Cancer Findings

Gene	Finding	Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***	NTRK2	None detected
ERBB2	None detected	NTRK3	None detected
KRAS	None detected	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected

Genomic Alteration	Finding
Microsatellite Status	***Microsatellite stable***
Tumor Mutational Burden	***4.73 Mut/Mb measured***

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

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 19.42% Locus: chr7:140453136 Transcript: NM_004333.6	**cetuximab + encorafenib** [1, 2 / I, II+] **cetuximab + encorafenib + chemotherapy** [1 / I, II+] **dabrafenib + trametinib** [1] encorafenib + panitumumab [I, II+] encorafenib + panitumumab + chemotherapy [I, II+] bevacizumab + chemotherapy [I]	**binimetinib + encorafenib** [1, 2 / I, II+] **cobimetinib + vemurafenib** [1, 2 / I, II+] **dabrafenib** [1, 2 / I, II+] **dabrafenib + trametinib** [1, 2 / I, II+] **vemurafenib** [1, 2 / I, II+] **atezolizumab + cobimetinib + vemurafenib** [1 / II+] **trametinib** [1, 2] cetuximab + encorafenib [I, II+] cetuximab + encorafenib + chemotherapy [I, II+] encorafenib [I, II+] encorafenib + panitumumab [I, II+]	35

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
			encorafenib + panitumumab + chemotherapy [I, II+] ipilimumab + nivolumab [I, II+] anti-PD-1 [II+] dabrafenib + pembrolizumab + trametinib [II+] ipilimumab [II+] nivolumab [II+] nivolumab + relatlimab [II+] pembrolizumab [II+] dabrafenib + MEK inhibitor selumetinib	
	Prognostic significance: ESMO: Poor			
IIC	*Microsatellite stable*	None*	None*	5
IIC	*FANCM deletion* FA complementation group M Locus: chr14:45605157	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	None*	None*	1
IIC	*TP53 p.(R273H) c.818G>A* tumor protein p53 Allele Frequency: 64.35% Locus: chr17:7577120 Transcript: NM_000546.6	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
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

BRAF p.(V600E) c.1799T>A	**binimetinib + cetuximab + encorafenib** [1] **plixorafenib** [1]

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.(Q223) c.667C>T, APC p.(R499*) c.1495C>T, MAP2K4 deletion, MLH3 deletion, PARP2 deletion, PPP2R2A deletion, RAD51B deletion, XRCC3 deletion, HLA-A deletion, HLA-B deletion, DICER1 deletion, GPS2 deletion, NCOR1 deletion, DSC3 deletion, DSC1 deletion, SMAD2 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	19.42%	NM_004333.6	missense
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	64.35%	NM_000546.6	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
APC	p.(Q223*)	c.667C>T	.	chr5:112128164	32.97%	NM_000038.6	nonsense
APC	p.(R499*)	c.1495C>T	COSM29364	chr5:112162891	35.11%	NM_000038.6	nonsense
PTPRZ1	p.(T1359I)	c.4076C>T	.	chr7:121653176	51.42%	NM_002851.3	missense
OR5D18	p.(H270C)	c.808_809delCAinsTG	.	chr11:55587913	3.89%	NM_001001952.1	missense
NOTCH3	p.(R1288W)	c.3862C>T	.	chr19:15288877	45.62%	NM_000435.3	missense
MEF2B	p.(P287S)	c.859C>T	.	chr19:19257104	71.59%	NM_001145785.2	missense
TOP1	p.(M699del)	c.2096_2098delTGA	.	chr20:39750692	18.52%	NM_003286.4	nonframeshift Deletion
RBM10	p.(?)	c.2295+1G>A	.	chrX:47044604	88.33%	NM_001204468.1	unknown
IRS4	p.(P637S)	c.1909C>T	.	chrX:107977666	99.89%	NM_003604.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
FANCM	chr14:45605157	1.15	0.66
SMAD4	chr18:48573387	1.11	0.64
MAP2K4	chr17:11924164	1.23	0.69
MLH3	chr14:75483761	1.11	0.64
PARP2	chr14:20811781	1.15	0.66
PPP2R2A	chr8:26149298	0.56	0.42
RAD51B	chr14:68290164	1.21	0.69
XRCC3	chr14:104165043	1.19	0.67
HLA-A	chr6:29910229	1.09	0.64
HLA-B	chr6:31322252	1.06	0.63
DICER1	chr14:95556791	1.11	0.65
GPS2	chr17:7216071	1.05	0.62
NCOR1	chr17:15935586	1.13	0.65
DSC3	chr18:28574139	1.16	0.67
DSC1	chr18:28710424	1	0.6
SMAD2	chr18:45368152	1.1	0.64
FOXA1	chr14:38060550	1.1	0.64
MAX	chr14:65472833	1.2	0.68
YES1	chr18:724481	1	0.6
SETBP1	chr18:42281265	0.95	0.58
BCL2	chr18:60795830	1.01	0.61

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ASXL1	chr20:30954155	5.74	2.5

Biomarker Descriptions

BRAF p.(V600E) c.1799T>A

B-Raf proto-oncogene, serine/threonine kinase

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1(CRAF)[120]. BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[121,122]. BRAF mutations are categorized into three distinct functional classes, namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway[123]. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[123]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[123,124,125].

Alterations and prevalence: Somatic mutations in BRAF are observed in 59% of thyroid carcinoma, 53% of skin cutaneous melanoma, 12% of colorectal adenocarcinoma, 8% of lung adenocarcinoma, 5% of uterine corpus endometrial carcinoma, and 2-3% of bladder urothelial carcinoma, lung squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, diffuse large B-cell lymphoma, glioblastoma multiforme, uterine carcinosarcoma, and head and neck squamous cell carcinoma[7,8]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[124,126]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[124]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[124]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[127,128,129]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11, as well as additional codons flanking V600 in the activation loop[126]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[7,8]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[130,131,132,133,134]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[125,130,132]. Alterations in BRAF are rare in pediatric cancers, with the most predominant being the V600E mutation and the BRAF::KIAA1549 fusion, both of which are observed in low-grade gliomas[135]. Somatic mutations are observed in 6% of glioma and less than 1% of bone cancer (2 in 327 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[7,8]. Amplification of BRAF is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[7,8].

Potential relevance: Vemurafenib[136] (2011) is the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, and it is also approved for BRAF V600E-positive Erdheim-Chester Disease (2017). BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[124]. BRAF kinase inhibitors including dabrafenib[137] (2013) and encorafenib[138] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[138] is approved in combination with cetuximab[139] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[124]. The MEK inhibitors, trametinib[140] (2013) and binimetinib[141] (2018), were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC[142]. The combinations of dabrafenib/trametinib[140](2015) and vemurafenib/cobimetinib[143] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017), children with low-grade gliomas, and children and adults with solid tumors (2022) harboring a BRAF V600E mutation[137]. The PD-L1 antibody, atezolizumab[144], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The FDA has granted fast track designation (2023) to ABM-1310[145] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[146] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[147] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[148], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. The FDA also granted fast track designation (2023) to the BRAF inhibitor, plixorafenib (PLX-8394)[149], for BRAF Class I (V600) and Class II (including fusions) altered cancer patients who have already undergone previous treatments. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[150]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification, alternative splice transcripts, as well as activation of PI3K signaling

Biomarker Descriptions (continued)

and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[151,152,153,154,155,156,157]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[134].

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[158]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[159,160]. 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[161]. 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[162]. 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)[162]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[163,164,165,166,167]. 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[160]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[159,160,164,168].

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[159,160,169,170]. 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[169,170].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[171] (2014) and nivolumab[172] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[171] 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[171]. Dostarlimab[173] (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[165,174]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[175] (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[165,176,177]. 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[177]. 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[178,179]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[178,179].

FANCM deletion

FA complementation group M

Background: The FANCM gene encodes the FA complementation group M protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[9,10]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[9]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[11,12]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[13,14]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[15,16].

Alterations and prevalence: Somatic mutations in FANCM are observed in 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% colorectal adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for FANCM aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCM are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[17].

Biomarker Descriptions (continued)

SMAD4 deletion

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[78,79]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[79,80,81]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[78,79]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[78]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[8,81,82]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[7,8,83].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[79,81,84,85,86]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[87,88]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[88]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[89].

TP53 p.(R273H) c.818G>A

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[90]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[91]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[92,93].

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%)[7,8,94,95,96,97]. 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[7,8]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[98,99,100,101]. Alterations in TP53 are also observed in pediatric cancers[7,8]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[7,8]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[7,8].

Potential relevance: The small molecule p53 reactivator, PC14586[102] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[103], (2019) and breakthrough designation[104] (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[105,106]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[107]. 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)[108,109,110,111,112,113]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[114]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[115].

Biomarker Descriptions (continued)

APC p.(Q223*) c.667C>T, APC p.(R499*) c.1495C>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[180]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[181,182]. 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[180,183]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[184].

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[7,8,83]. 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[185,186].

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

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[66]. Activation of MAPK proteins occurs through a kinase signaling cascade[66,67,68]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[66,67,68]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[66,67,68]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[69].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[7,8]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[7,8]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[70,71].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[33]. MLH3 is considered a mismatch repair (MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[33,34,35]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[36].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[7,8]. Biallelic deletions are observed in 2% of kidney chromophobe[7,8].

Potential relevance: Currently, no therapies are approved for MLH3 aberrations.

PARP2 deletion

poly(ADP-ribose) polymerase 2

Background: The PARP2 gene encodes the poly(ADP-ribose) polymerase 2 protein[1]. PARP2 belongs to the large PARP protein family that also includes PARP1, PARP3, and PARP4[37]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[37,38]. PARP enzymes are involved in several DNA repair pathways[37,38]. PARP2 interacts with PARP1 to assist in repair of single-strand breaks through base excision repair (BER)[37,39]. PARP2 has also been observed to promote homologous recombination repair (HRR) of double-strand breaks (DSBs) over non-homologous end joining (NHEJ) by limiting the accumulation of TP53BP1 and preventing TP53BP1 from blocking HRR resection of DNA[39,40]. PARylation of

Biomarker Descriptions (continued)

histones H1, H2A, and H2B by PARP2 promotes an open chromatin conformation, which allows DNA repair machinery access to sites of DNA damage[41].

Alterations and prevalence: Somatic mutations in PARP2 are observed in 4% of uterine corpus endometrial carcinoma, and uterine carcinosarcoma, and 2% of stomach adenocarcinoma, and skin cutaneous melanoma[7,8].

Potential relevance: Currently, no therapies are approved for PARP2 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[42,43]. Although not indicated for specific alterations in PARP2, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[44] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, 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 BRCA1. Rucaparib[45] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[46] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[47] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

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)[18,19]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[20]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[18].

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[18,19,21,22]. 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[7].

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[23], 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[18]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[24].

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[72]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[73]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[74]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[13,75]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[76]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[77].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[7,8]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[77].

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 RAD51B. In 2022, the FDA granted fast

Biomarker Descriptions (continued)

track designation to the small molecule inhibitor, pidnarulex[23], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,25]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[25,26]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[27].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[7,8]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[27].

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[60]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[61]. 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[62,63,64]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[65].

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[7,8]. Biallelic loss of HLA-A is observed in 4% of DLBCL[7,8].

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

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[60]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[61]. 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[62,63,64]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[65].

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[7,8]. Biallelic loss of HLA-B is observed in 5% of DLBCL[7,8].

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

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[48]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[48,49]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[48]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[48,49]. miRNAs are

Biomarker Descriptions (continued)

frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[49,50,51,52]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[53].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, and 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[7,8]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% kidney chromophobe[7,8].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[54]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[54,55]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[56,57,58].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[7,8]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[7,8]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[7,8,59]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[59].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,28,29]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[28,29,30,31]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[29]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[29,32].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[7,8]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[7,8]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

DSC3 deletion

desmocollin 3

Background: The DSC3 gene encodes desmocollin 3, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC1 and DSC2[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[2]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[3]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC3 in tumorigenesis[2,4,5,6].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in DSC3 are observed in 19% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, and 3% of bladder urothelial carcinoma[7,8]. Biallelic deletion of DSC3 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[7,8].

Potential relevance: Currently, no therapies are approved for DSC3 aberrations.

DSC1 deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[2]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[3]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis[2,4,5,6].

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma[7,8]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[7,8].

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

SMAD2 deletion

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes[1,78,79]. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[78,79]. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF-β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development[79]. Following activation of type I TGF-β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes[116,117]. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2[117,118].

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma[7,8]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[7,8,117]. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex[7,8,119]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[7,8].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. For the most up-to-date information, search www.fda.gov.

BRAF p.(V600E) c.1799T>A

binimetinib + cetuximab + encorafenib

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the MEK inhibitor, binimetinib, in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer.

Reference:

https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791

plixorafenib

Cancer type: Solid Tumor

Variant class: BRAF V600 mutation

Supporting Statement:
The FDA has granted Fast Track designation to a novel small molecule inhibitor, plixorafenib (PLX-8394), for the treatment of patients with cancers harboring BRAF Class 1 (V600) and Class 2 (including fusions) alterations who have exhausted prior therapies.

Reference:

https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/

ABM-1310

Cancer type: Glioblastoma IDH-wildtype (Grade 4)

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Fast Track designation to ABM-1310 for the treatment of glioblastoma (GBM) patients with BRAF V600E mutation.

Reference:

https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html

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,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed 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

BRAF p.(V600E) c.1799T>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + trametinib	◑	○	○	○	✖
cetuximab + encorafenib	●	◑	●	●	✖
cetuximab + encorafenib + FOLFOX	●	◑	✖	✖	✖
cobimetinib + vemurafenib	○	○	○	○	● (II/III)
binimetinib + encorafenib	○	○	○	○	✖
dabrafenib	○	○	○	✖	● (II)
vemurafenib	○	○	○	✖	✖
atezolizumab + cobimetinib + vemurafenib	○	○	✖	✖	✖
trametinib	○	✖	○	✖	✖
encorafenib + panitumumab	✖	◑	✖	✖	✖
encorafenib + panitumumab + FOLFOX	✖	◑	✖	✖	✖
encorafenib	✖	○	✖	○	✖
dabrafenib + pembrolizumab + trametinib	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
bevacizumab + CAPOX	✖	✖	✖	●	✖
bevacizumab + FOLFOX	✖	✖	✖	●	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	●	✖
anti-PD-1	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
nivolumab	✖	✖	✖	○	✖
nivolumab + relatlimab	✖	✖	✖	○	✖
pembrolizumab	✖	✖	✖	○	✖
encorafenib, binimetinib, cetuximab	✖	✖	✖	✖	● (III)
cetuximab, binimetinib, encorafenib	✖	✖	✖	✖	● (II/III)
bevacizumab, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, chemotherapy, leucovorin	✖	✖	✖	✖	● (II)
camrelizumab, regorafenib, fruquintinib	✖	✖	✖	✖	● (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

BRAF p.(V600E) c.1799T>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab, encorafenib	✖	✖	✖	✖	● (II)
cetuximab, encorafenib, binimetinib	✖	✖	✖	✖	● (II)
cetuximab, panitumumab, encorafenib, antimalarial	✖	✖	✖	✖	● (II)
cetuximab, vemurafenib, chemotherapy	✖	✖	✖	✖	● (II)
encorafenib, cetuximab, bevacizumab	✖	✖	✖	✖	● (II)
encorafenib, cetuximab, chemotherapy	✖	✖	✖	✖	● (II)
KN046, regorafenib	✖	✖	✖	✖	● (II)
tunlametinib, vemurafenib	✖	✖	✖	✖	● (II)
vemurafenib, cetuximab, chemotherapy	✖	✖	✖	✖	● (II)
vemurafenib, cetuximab, chemotherapy, bevacizumab	✖	✖	✖	✖	● (II)
chemotherapy, KSQ-004, aldesleukin	✖	✖	✖	✖	● (I/II)
donafenib, trametinib, cetuximab, chemotherapy	✖	✖	✖	✖	● (I/II)
RX208, serplulimab	✖	✖	✖	✖	● (I/II)
RX208, trametinib	✖	✖	✖	✖	● (I/II)
exarafenib, binimetinib	✖	✖	✖	✖	● (I)
HSK42360	✖	✖	✖	✖	● (I)
IK-595	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
PF-07799933, cetuximab, binimetinib	✖	✖	✖	✖	● (I)
RMC-6236	✖	✖	✖	✖	● (I)
RO-7276389, cobimetinib	✖	✖	✖	✖	● (I)
RX208	✖	✖	✖	✖	● (I)
ulixertinib, cetuximab, encorafenib	✖	✖	✖	✖	● (I)
ZEN-3694, binimetinib	✖	✖	✖	✖	● (I)
ZEN-3694, cetuximab, encorafenib	✖	✖	✖	✖	● (I)

Microsatellite stable

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
encorafenib, binimetinib, cetuximab	✖	✖	✖	✖	● (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

Microsatellite stable (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
camrelizumab, regorafenib, fruquintinib	✖	✖	✖	✖	● (II)
cetuximab, encorafenib, binimetinib	✖	✖	✖	✖	● (II)
encorafenib, cetuximab, bevacizumab	✖	✖	✖	✖	● (II)
KN046, regorafenib	✖	✖	✖	✖	● (II)

FANCM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

SMAD4 deletion

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

TP53 p.(R273H) c.818G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (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
RAD51B	***CNV, CN:1.21***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Chidgey et al. Desmosomes: a role in cancer?. Br J Cancer. 2007 Jun 18;96(12):1783-7. PMID: 17519903
3. Dubash et al. Desmosomes. Curr Biol. 2011 Jul 26;21(14):R529-31. PMID: 21783027
4. Hardman et al. Desmosomal cadherin misexpression alters beta-catenin stability and epidermal differentiation. Mol Cell Biol. 2005 Feb;25(3):969-78. PMID: 15657425
5. Wang et al. Lower DSC1 expression is related to the poor differentiation and prognosis of head and neck squamous cell carcinoma (HNSCC). J Cancer Res Clin Oncol. 2016 Dec;142(12):2461-2468. PMID: 27601166
6. Oshiro et al. Epigenetic silencing of DSC3 is a common event in human breast cancer. Breast Cancer Res. 2005;7(5):R669-80. PMID: 16168112
7. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
8. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
9. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047
10. Rodríguez et al. Fanconi anemia pathway. Curr Biol. 2017 Sep 25;27(18):R986-R988. PMID: 28950089
11. Garcia-Higuera et al. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol. Cell. 2001 Feb;7(2):249-62. PMID: 11239454
12. Hussain et al. Direct interaction of FANCD2 with BRCA2 in DNA damage response pathways. Hum. Mol. Genet. 2004 Jun 15;13(12):1241-8. PMID: 15115758
13. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
14. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
15. Michl et al. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. EMBO J. 2016 May 2;35(9):909-23. PMID: 27037238
16. Abbasi et al. A rare FANCA gene variation as a breast cancer susceptibility allele in an Iranian population. Mol Med Rep. 2017 Jun;15(6):3983-3988. PMID: 28440412
17. Stoepker et al. DNA helicases FANCM and DDX11 are determinants of PARP inhibitor sensitivity. DNA Repair (Amst). 2015 Feb;26:54-64. PMID: 25583207
18. Kalev et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. Cancer Res. 2012 Dec 15;72(24):6414-24. PMID: 23087057
19. Álvarez-Fernández et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. Cell Death Differ. 2018 May;25(5):828-840. PMID: 29229993
20. Perrotti et al. Protein phosphatase 2A: a target for anticancer therapy. Lancet Oncol. 2013 May;14(6):e229-38. PMID: 23639323
21. Beca et al. Altered PPP2R2A and Cyclin D1 Expression Defines a Subgroup of Aggressive Luminal-Like Breast Cancer. BMC Cancer. 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. PMID: 25879784
22. Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52. PMID: 22522925
23. https://www.senhwabio.com//en/news/20220125
24. NCCN Guidelines® - NCCN-Prostate Cancer [Version 2.2025]
25. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015 Apr 1;7(4):a016600. PMID: 25833843
26. Liu et al. Role of RAD51C and XRCC3 in genetic recombination and DNA repair. J Biol Chem. 2007 Jan 19;282(3):1973-9. PMID: 17114795
27. Wilson et al. FANCG promotes formation of a newly identified protein complex containing BRCA2, FANCD2 and XRCC3. Oncogene. 2008 Jun 12;27(26):3641-52. PMID: 18212739
28. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. Front Immunol. 2020;11:569358. PMID: 33117357
29. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. Pharmacol Res. 2016 Jun;108:75-79. PMID: 27149915
30. Bhaskara et al. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell. 2010 Nov 16;18(5):436-47. PMID: 21075309

References (continued)

31. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. Genes Dev. 2013 Apr 15;27(8):819-35. PMID: 23630073
32. Noblejas-López et al. Evaluation of transcriptionally regulated genes identifies NCOR1 in hormone receptor negative breast tumors and lung adenocarcinomas as a potential tumor suppressor gene. PLoS One. 2018;13(11):e0207776. PMID: 30485330
33. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
34. Kadyrova et al. Human MutLγ, the MLH1-MLH3 heterodimer, is an endonuclease that promotes DNA expansion. Proc Natl Acad Sci U S A. 2020 Feb 18;117(7):3535-3542. PMID: 32015124
35. Al-Sweel et al. mlh3 mutations in baker's yeast alter meiotic recombination outcomes by increasing noncrossover events genome-wide. PLoS Genet. 2017 Aug;13(8):e1006974. PMID: 28827832
36. Narayanan et al. Tumor Infiltrating Lymphocytes and Macrophages Improve Survival in Microsatellite Unstable Colorectal Cancer. Sci Rep. 2019 Sep 17;9(1):13455. PMID: 31530839
37. Amé et al. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93. PMID: 15273990
38. Morales et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr. 2014;24(1):15-28. PMID: 24579667
39. Fouquin et al. PARP2 controls double-strand break repair pathway choice by limiting 53BP1 accumulation at DNA damage sites and promoting end-resection. Nucleic Acids Res. 2017 Dec 1;45(21):12325-12339. PMID: 29036662
40. Daley et al. 53BP1, BRCA1, and the choice between recombination and end joining at DNA double-strand breaks. Mol Cell Biol. 2014 Apr;34(8):1380-8. PMID: 24469398
41. Schreiber et al. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006 Jul;7(7):517-28. PMID: 16829982
42. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
43. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
48. Aharoni et al. Dynamical comparison between Drosha and Dicer reveals functional motion similarities and dissimilarities. PLoS One. 2019;14(12):e0226147. PMID: 31821368
49. Lee et al. MicroRNAs in cancer. Annu Rev Pathol. 2009;4:199-227. PMID: 18817506
50. Hammond. An overview of microRNAs. Adv Drug Deliv Rev. 2015 Jun 29;87:3-14. PMID: 25979468
51. Wen et al. Biosci Rep. 2018 Jun 29;38(3). PMID: 29654164
52. Kumar et al. Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet. 2007 May;39(5):673-7. PMID: 17401365
53. Robertson et al. DICER1 Syndrome: DICER1 Mutations in Rare Cancers. Cancers (Basel). 2018 May 15;10(5). PMID: 29762508
54. Cheng et al. G protein pathway suppressor 2 (GPS2) is a transcriptional corepressor important for estrogen receptor alpha-mediated transcriptional regulation. J Biol Chem. 2009 Dec 25;284(52):36395-36404. PMID: 19858209
55. Si et al. G protein pathway suppressor 2 suppresses gastric cancer by destabilizing epidermal growth factor receptor. Cancer Sci. 2021 Dec;112(12):4867-4882. PMID: 34609770
56. Bien-Willner et al. Mutation and expression analysis in medulloblastoma yields prognostic variants and a putative mechanism of disease for i17q tumors. Acta Neuropathol Commun. 2014 Jul 17;2:74. PMID: 25030029
57. Huang et al. G protein pathway suppressor 2 (GPS2) acts as a tumor suppressor in liposarcoma. Tumour Biol. 2016 Oct;37(10):13333-13343. PMID: 27460081
58. Chan et al. Loss of G-Protein Pathway Suppressor 2 Promotes Tumor Growth Through Activation of AKT Signaling. Front Cell Dev Biol. 2020;8:608044. PMID: 33490071
59. O'Meara et al. Identification of an MLL4-GPS2 fusion as an oncogenic driver of undifferentiated spindle cell sarcoma in a child. Genes Chromosomes Cancer. 2014 Dec;53(12):991-8. PMID: 25139254
60. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
61. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204

References (continued)

62. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
63. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
64. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
65. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675
66. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. Clin. Cancer Res. 2013 May 1;19(9):2301-9. PMID: 23406774
67. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3). PMID: 32046099
68. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 2014 Jan;171(1):24-37. PMID: 24117156
69. Ahn et al. Map2k4 functions as a tumor suppressor in lung adenocarcinoma and inhibits tumor cell invasion by decreasing peroxisome proliferator-activated receptor γ2 expression. Mol. Cell. Biol. 2011 Nov;31(21):4270-85. PMID: 21896780
70. Robinson et al. Mitogen-activated protein kinase kinase 4/c-Jun NH2-terminal kinase kinase 1 protein expression is subject to translational regulation in prostate cancer cell lines. Mol. Cancer Res. 2008 Mar;6(3):501-8. PMID: 18337456
71. Xue et al. MAP3K1 and MAP2K4 mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. Cell Res. 2018 Jul;28(7):719-729. PMID: 29795445
72. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. Genes (Basel). 2018 Dec 13;9(12). PMID: 30551670
73. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. Semin. Cell Dev. Biol. 2011 Oct;22(8):898-905. PMID: 21821141
74. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. Mol. Cell. Biol. 2013 Jan;33(2):387-95. PMID: 23149936
75. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. Endocr. Relat. Cancer. 2016 Jun;23(6):R267-85. PMID: 27226207
76. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. Cancer Res. 2006 Jun 15;66(12):6018-24. PMID: 16778173
77. Pelttari et al. RAD51B in Familial Breast Cancer. PLoS ONE. 2016;11(5):e0153788. PMID: 27149063
78. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. J Clin Med. 2017 Jan 5;6(1). PMID: 28067794
79. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 2018;14(2):111-123. PMID: 29483830
80. Cicenas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. Cancers (Basel). 2017 Apr 28;9(5). PMID: 28452926
81. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. Biochem. Biophys. Res. Commun. 2003 Jul 11;306(4):799-804. PMID: 12821112
82. Mehrvarz et al. Association of SMAD4 mutation with patient demographics, tumor characteristics, and clinical outcomes in colorectal cancer. PLoS ONE. 2017;12(3):e0173345. PMID: 28267766
83. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
84. Yan et al. Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer. Clin. Cancer Res. 2016 Jun 15;22(12):3037-47. PMID: 26861460
85. Voorneveld et al. A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer. Transl Oncol. 2015 Feb;8(1):18-24. PMID: 25749173
86. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. Transl Oncol. 2016 Feb;9(1):1-7. PMID: 26947875
87. Boulay et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. Br. J. Cancer. 2002 Sep 9;87(6):630-4. PMID: 12237773
88. Kozak et al. Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer. J. Clin. Pathol. 2015 May;68(5):341-5. PMID: 25681512

References (continued)

89. Ozawa et al. SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells. Clin. Cancer Res. 2017 Sep 1;23(17):5162-5175. PMID: 28522603
90. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
91. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
92. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602
93. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
94. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
95. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
96. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
97. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
98. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217
99. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514
100. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424
101. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566
102. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html
103. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation
104. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167
105. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
106. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
107. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. PMID: 34185076
108. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
109. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
110. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
111. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]
112. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]
113. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 3.2024]
114. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]
115. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829
116. Massagué et al. Smad transcription factors. Genes Dev. 2005 Dec 1;19(23):2783-810. PMID: 16322555
117. Fleming et al. SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. Cancer Res. 2013 Jan 15;73(2):725-35. PMID: 23139211
118. Fukuchi et al. Lack of activated Smad2 in transforming growth factor-beta signaling is an unfavorable prognostic factor in patients with esophageal squamous cell carcinoma. J Surg Oncol. 2006 Jul 1;94(1):51-6. PMID: 16788944

References (continued)

119. Galka-Marciniak et al. A pan-cancer atlas of somatic mutations in miRNA biogenesis genes. Nucleic Acids Res. 2021 Jan 25;49(2):601-620. PMID: 33406242
120. Yuryev et al. The RAF family: an expanding network of post-translational controls and protein-protein interactions. Cell Res. 1998 Jun;8(2):81-98. PMID: 9669024
121. Cheng et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod. Pathol. 2018 Jan;31(1):24-38. PMID: 29148538
122. Alrabadi et al. Detection of driver mutations in BRAF can aid in diagnosis and early treatment of dedifferentiated metastatic melanoma. Mod. Pathol. 2019 Mar;32(3):330-337. PMID: 30315274
123. Quan et al. The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients. Journal of Translational Medicine, 29 Aug 2019, 17(1):298. PMID: 31470866
124. Yao et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature. 2017 Aug 10;548(7666):234-238. PMID: 28783719
125. Bracht et al. BRAF Mutations Classes I, II, and III in NSCLC Patients Included in the SLLIP Trial: The Need for a New Pre-Clinical Treatment Rationale. Cancers (Basel). 2019 Sep 17;11(9). PMID: 31533235
126. Wan et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004 Mar 19;116(6):855-67. PMID: 15035987
127. Tiacci et al. BRAF mutations in hairy-cell leukemia. N. Engl. J. Med. 2011 Jun 16;364(24):2305-15. PMID: 21663470
128. Diamond et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875
129. Imielinski et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014 Apr;124(4):1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PMID: 24569458
130. Ciampi et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J. Clin. Invest. 2005 Jan;115(1):94-101. PMID: 15630448
131. Palanisamy et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat. Med. 2010 Jul;16(7):793-8. PMID: 20526349
132. Jones et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res. 2008 Nov 1;68(21):8673-7. PMID: 18974108
133. Cin et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. Acta Neuropathol. 2011 Jun;121(6):763-74. doi: 10.1007/s00401-011-0817-z. Epub 2011 Mar 20. PMID: 21424530
134. Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. Int. J. Cancer. 2016 Feb 15;138(4):881-90. PMID: 26314551
135. Tan et al. Paediatric Gliomas: BRAF and Histone H3 as Biomarkers, Therapy and Perspective of Liquid Biopsies. Cancers (Basel). 2021 Feb 4;13(4). PMID: 33557011
136. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
137. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/202806s038,217514s009lbl.pdf
138. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210496s018lbl.pdf
139. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
140. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204114s038,217513s009lbl.pdf
141. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210498s011lbl.pdf
142. Subbiah et al. Clinical Development of BRAF plus MEK Inhibitor Combinations. Trends Cancer. 2020 Sep;6(9):797-810. PMID: 32540454
143. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
144. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761034s053lbl.pdf
145. https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html
146. https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791
147. https://biomed-valley.com/news/#press-releases
148. https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food

References (continued)

149. https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/
150. Kulkarni et al. BRAF Fusion as a Novel Mechanism of Acquired Resistance to Vemurafenib in BRAFV600E Mutant Melanoma. Clin. Cancer Res. 2017 Sep 15;23(18):5631-5638. PMID: 28539463
151. Johnson et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur. J. Cancer. 2015 Dec;51(18):2792-9. PMID: 26608120
152. Nazarian et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626. Epub 2010 Nov 24. PMID: 21107323
153. Rizos et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin. Cancer Res. 2014 Apr 1;20(7):1965-77. PMID: 24463458
154. Shi et al. A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition. Cancer Discov. 2014 Jan;4(1):69-79. PMID: 24265152
155. Van et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov. 2014 Jan;4(1):94-109. doi: 10.1158/2159-8290.CD-13-0617. Epub 2013 Nov 21. PMID: 24265153
156. Villanueva et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. Cell Rep. 2013 Sep 26;4(6):1090-9. PMID: 24055054
157. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov. 2014 Jan;4(1):80-93. PMID: 24265155
158. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
159. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. Front Oncol. 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
160. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
161. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. Front Microbiol. 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
162. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57. PMID: 9823339
163. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. Cancer Res. 2002 Jan 1;62(1):53-7. PMID: 11782358
164. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
165. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
166. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
167. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. Medicine (Baltimore). 2015 Dec;94(50):e2260. PMID: 26683947
168. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. J. Clin. Oncol. 2019 Feb 1;37(4):286-295. PMID: 30376427
169. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. Nat Commun. 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
170. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
171. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
172. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
173. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
174. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
175. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
176. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N. Engl. J. Med. 2003 Jul 17;349(3):247-57. PMID: 12867608
177. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann. Oncol. 2015 Jan;26(1):126-32. PMID: 25361982
178. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522

References (continued)

179. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031

180. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell. Physiol. Biochem. 2018;51(6):2647-2693. PMID: 30562755

181. Stamos et al. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a007898. PMID: 23169527

182. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. Mol Cancer. 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464

183. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J. Cell. Sci. 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494

184. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum. Mol. Genet. 1992 Jul;1(4):229-33. PMID: 1338904

185. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc. Natl. Acad. Sci. U.S.A. 2000 Mar 28;97(7):3352-7. PMID: 10737795

186. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. Nucleic Acids Res. 1998 Jan 1;26(1):269-70. PMID: 9399850