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

Patient Name: 박경래
Gender: M
Sample ID: N25-138

Primary Tumor Site: Colon
Collection Date: 2025.07.25

Sample Cancer Type: Colon Cancer

Table of Contents	Page

Report Highlights
3 Relevant Biomarkers
32 Therapies Available
107 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 instability-High***
Tumor Mutational Burden	***22.9 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	*Microsatellite instability-High*	**ipilimumab + nivolumab** [1, 2 / I, II+] **nivolumab** [1 / I, II+] **pembrolizumab** [1, 2 / I, II+] cemiplimab [I, II+] dostarlimab [I, II+] retifanlimab [I, II+] tislelizumab [I, II+] toripalimab [I, II+]	**dostarlimab** [2 / I, II+] **ipilimumab + nivolumab** [2 / I, II+] **pembrolizumab** [1, 2 / I, II+] **dostarlimab + chemotherapy** [2] cemiplimab [I, II+] nivolumab [I, II+] retifanlimab [I, II+] tislelizumab [I, II+] toripalimab [I, II+] nivolumab + chemotherapy [I] pembrolizumab + chemotherapy [I] avelumab [II+]	80

*** 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
			durvalumab + tremelimumab [II+]	
	Prognostic significance: NCCN: Good, ESMO: Very low			
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 35.54% 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+] 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	30
	Prognostic significance: ESMO: Poor			
IIC	*TP53 p.(R273H) c.818G>A* tumor protein p53 Allele Frequency: 5.45% 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

Microsatellite instability-High	**ATX-559** [1]
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

KMT2D p.(R5214C) c.15640C>T, TP53 p.(R273C) c.817C>T, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-A p.(Q204) c.610C>T, TNFAIP3 p.(R183*) c.547C>T, NQO1 p.(P187S) c.559C>T, NCOR1 p.(V1444Cfs*9) c.4330delG, 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	35.54%	NM_004333.6	missense
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	5.45%	NM_000546.6	missense
KMT2D	p.(R5214C)	c.15640C>T	.	chr12:49420109	5.75%	NM_003482.4	missense
TP53	p.(R273C)	c.817C>T	COSM10659	chr17:7577121	7.65%	NM_000546.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	27.53%	NM_000463.3	missense
HLA-A	p.(Q204*)	c.610C>T	.	chr6:29911311	23.95%	NM_001242758.1	nonsense
TNFAIP3	p.(R183*)	c.547C>T	.	chr6:138196885	5.70%	NM_001270507.2	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.30%	NM_000903.3	missense
NCOR1	p.(V1444Cfs*9)	c.4330delG	.	chr17:15973661	21.62%	NM_006311.4	frameshift Deletion
PGD	p.(R70W)	c.208C>T	.	chr1:10460573	20.56%	NM_002631.4	missense
RWDD3	p.(C80S)	c.238T>A	.	chr1:95709919	22.16%	NM_015485.5	missense
PARP1	p.(A410V)	c.1229C>T	.	chr1:226568840	22.24%	NM_001618.4	missense
KIAA1841	p.(?)	c.670+3delA	.	chr2:61304295	47.70%	NM_001129993.3	unknown
NFE2L2	p.(V523del)	c.1568_1570delTAG	.	chr2:178095760	43.94%	NM_006164.5	nonframeshift Deletion
MAP3K1	p.(H1361R)	c.4082A>G	.	chr5:56181858	21.97%	NM_005921.2	missense
ADAMTS2	p.(P224A)	c.670C>G	.	chr5:178699930	18.44%	NM_014244.5	missense
FLT4	p.(V627A)	c.1880T>C	.	chr5:180048682	22.31%	NM_182925.5	missense
LATS1	p.(A20V)	c.59C>T	.	chr6:150023204	21.75%	NM_004690.4	missense
KMT2C	p.(I3360V)	c.10078A>G	.	chr7:151860584	38.35%	NM_170606.3	missense
CSMD3	p.(P3236H)	c.9707C>A	.	chr8:113276023	15.57%	NM_198123.2	missense
FGF4	p.(V69I)	c.205G>A	.	chr11:69589648	7.21%	NM_002007.4	missense
CBL	p.(L272*)	c.815delT	.	chr11:119145603	23.22%	NM_005188.4	nonsense
FGF23	p.(A141V)	c.422C>T	.	chr12:4479843	21.52%	NM_020638.3	missense
KMT2D	p.(P4186S)	c.12556C>T	.	chr12:49425932	23.55%	NM_003482.4	missense
TBX3	p.(D177N)	c.529G>A	.	chr12:115118812	22.66%	NM_016569.4	missense
LATS2	p.(R867M)	c.2600G>T	.	chr13:21555670	20.50%	NM_014572.3	missense
PARP4	p.(?)	c.3285_3285+5delinsAGT	.	chr13:25021149	100.00%	NM_006437.4	unknown
ADAMTS17	p.(V342G)	c.1025T>G	.	chr15:100801690	20.25%	NM_139057.4	missense
NCOR1	p.(M1297I)	c.3891G>A	.	chr17:15975463	20.58%	NM_006311.4	missense
MYCBPAP	p.(P660S)	c.1978C>T	.	chr17:48603437	54.21%	NM_032133.6	missense
BRIP1	p.([E879=;S880P])	c.2637_2638delATinsGC	.	chr17:59763464	5.00%	NM_032043.3	synonymous, missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
SMARCA4	p.(P647L)	c.1940C>T	.	chr19:11113832	21.96%	NM_001128849.3	missense
CCNE1	p.(P104L)	c.311C>T	.	chr19:30308174	21.58%	NM_001238.4	missense
RBM10	p.(L983P)	c.2948T>C	.	chrX:47045958	3.35%	NM_001204468.1	missense
ZMYM3	p.(G401V)	c.1202G>T	.	chrX:70469925	40.50%	NM_201599.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-A	chr6:29910229	0	0.53

Biomarker Descriptions

Microsatellite instability-High

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[10]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[11,12]. MSI is closely tied to the status of the mismatch repair (MMR) genes[13]. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[13]. 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[14]. 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)[14]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[15,16,17,18,19]. 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[12]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[11,12,16,20].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[11,12,21,22]. 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[21,22]. MSI-H is rare in pediatric solid tumors and is primarily observed in high grade gliomas, including astrocytoma and oligodendroglioma[23,24].

Potential relevance: Anti-PD-1 immune checkpoint inhibitor pembrolizumab[25] (2014) is approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[25] 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 in adults and children who have progressed following treatment, with no alternative options, making it the first anti-PD-1 inhibitor to be approved with a tumor-agnostic indication[25]. Dostarlimab[26] (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 therapy option in several cancer types that are dMMR/MSI-H such as advanced or metastatic colon or rectal cancer[17,27,28,29,30,31,32,33,34,35]. Nivolumab[36] (2015) is approved as a single agent or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[37] (2011), for adults and children with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[17,38,39]. 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[39]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors, compared to those with MSI-H tumors[40,41]. However, combining checkpoint blockade with chemotherapy or targeted therapies has demonstrated responses in MSS or pMMR cancers[40,41].

Biomarker Descriptions (continued)

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)[76]. 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[77,78]. 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[79]. 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[79]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[79,80,81].

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[8,9]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[80,82]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[80]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[80]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[83,84,85]. 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[82]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[8,9]. 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[86,87,88,89,90]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[81,86,88]. 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[91]. 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)[8,9]. 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)[8,9].

Potential relevance: Vemurafenib[92] (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[80]. BRAF kinase inhibitors including dabrafenib[93] (2013) and encorafenib[94] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[94] is approved in combination with cetuximab[95] (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[80]. The MEK inhibitors, trametinib[96] (2013) and binimetinib[97] (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[98]. The combinations of dabrafenib/trametinib[96](2015) and vemurafenib/cobimetinib[99] (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[93]. The PD-L1 antibody, atezolizumab[100], 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[101] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[102] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[103] 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[104], 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)[105], 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[106]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification, alternative splice transcripts, as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[107,108,109,110,111,112,113]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[90].

TP53 p.(R273C) c.817C>T, 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[45]. Alterations in TP53 are required

Biomarker Descriptions (continued)

for oncogenesis as they result in loss of protein function and gain of transforming potential[46]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[47,48].

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%)[8,9,49,50,51,52]. 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[8,9]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[53,54,55,56]. Alterations in TP53 are also observed in pediatric cancers[8,9]. 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)[8,9]. 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)[8,9].

Potential relevance: The small molecule p53 reactivator, PC14586[57] (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[58], (2019) and breakthrough designation[59] (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[60,61]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[62]. 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)[63,64,65,66,67,68]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[69]. 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[70].

KMT2D p.(R5214C) c.15640C>T

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[114]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[114]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[114].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,115]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[115,116]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[117]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[117,118,119,120]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[121].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[8,9].

Biomarker Descriptions (continued)

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

HLA-A deletion, HLA-A p.(Q204*) c.610C>T

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[2]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[3]. 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[4,5,6]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[7].

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[8,9]. Biallelic loss of HLA-A is observed in 4% of DLBCL[8,9].

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

TNFAIP3 p.(R183*) c.547C>T

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[1]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[42]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[42,43]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[42]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[42,44].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[8,9]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[8,9,42].

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

NCOR1 p.(V1444Cfs*9) c.4330delG

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)[1,71,72]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[71,72,73,74]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[72]. 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[72,75].

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[8,9]. 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[8,9]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[8,9].

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

Microsatellite instability-High

dostarlimab

Cancer type: Rectal Cancer **Variant class:** Microsatellite instability-High

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the programmed death receptor-1 (PD-1)-blocking antibody, Jemperli (dostarlimab-gxly), for the treatment of patients with locally advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) rectal cancer.

Reference:

https://us.gsk.com//en-us/media/press-releases/jemperli-dostarlimab-gxly-receives-us-fda-breakthrough-therapy-designation-for-locally-advanced-dmmrmsi-h-rectal-cancer/

ATX-559

Cancer type: Colorectal Cancer **Variant class:** Microsatellite instability-High

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule DHX9 inhibitor, ATX-559, for the treatment of adult patients with unresectable/metastatic dMMR/MSI-H colorectal cancer post checkpoint inhibitor treatment.

Reference:

https://www.prnewswire.com/news-releases/accent-therapeutics-announces-first-patient-dosed-in-phase-12-trial-of-novel-kif18a-inhibitor-atx-295-and-receives-fda-fast-track-designation-for-lead-assets-atx-295-and-dhx9-inhibitor-atx-559-302427964.html

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

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

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

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-05-01. 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.

Microsatellite instability-High

pembrolizumab

Cancer type: Giant Cell Tumor of Soft Tissue **Variant class:** Microsatellite instability-High

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2025]

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed 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

Microsatellite instability-High

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	◑	◑	◑	◑	● (III)
ipilimumab + nivolumab	●	◑	◑	●	● (II)
nivolumab	●	◑	✖	✖	● (III)
dostarlimab	✖	◑	○	○	● (III)
cemiplimab	✖	◑	✖	✖	● (II)
tislelizumab	✖	◑	✖	✖	● (II)
retifanlimab	✖	◑	✖	✖	✖
toripalimab	✖	◑	✖	✖	✖
avelumab	✖	○	✖	✖	✖
durvalumab + tremelimumab	✖	○	✖	✖	✖
nivolumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
nivolumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
dostarlimab + carboplatin + paclitaxel	✖	✖	○	✖	✖
anti-PD-1, anti-PD-L1 antibody, anti-CTLA-4	✖	✖	✖	✖	● (III)
anti-PD-L1 antibody, anti-PD-1, anti-CTLA-4, angiogenesis inhibitor	✖	✖	✖	✖	● (III)
ipilimumab (Innovent Biologics), sintilimab	✖	✖	✖	✖	● (III)
nivolumab, ipilimumab	✖	✖	✖	✖	● (III)
PSB-205	✖	✖	✖	✖	● (III)
sintilimab	✖	✖	✖	✖	● (III)
tislelizumab, chemotherapy	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II/III)
anti-PD-1, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, anti-PD-1	✖	✖	✖	✖	● (II)
botensilimab, balstilimab	✖	✖	✖	✖	● (II)
botensilimab, balstilimab + botensilimab	✖	✖	✖	✖	● (II)
cadonilimab	✖	✖	✖	✖	● (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 instability-High (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
catequentinib, penpulimab	✖	✖	✖	✖	● (II)
catequentinib, tislelizumab	✖	✖	✖	✖	● (II)
cemiplimab, fianlimab	✖	✖	✖	✖	● (II)
dostarlimab, chemoradiation therapy	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
envafolimab	✖	✖	✖	✖	● (II)
KN046, regorafenib, apatinib	✖	✖	✖	✖	● (II)
nivolumab, durvalumab	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab, radiation therapy	✖	✖	✖	✖	● (II)
nivolumab, relatlimab	✖	✖	✖	✖	● (II)
nivolumab, rosiglitazone maleate, pembrolizumab, metformin hydrochloride	✖	✖	✖	✖	● (II)
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)
pembrolizumab, regorafenib	✖	✖	✖	✖	● (II)
sintilimab, ipilimumab (Innovent Biologics), lenvatinib, anti-PD-1, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
tinodasertib, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
tiragolumab, atezolizumab	✖	✖	✖	✖	● (II)
toripalimab, celecoxib	✖	✖	✖	✖	● (II)
AFM-24_I, atezolizumab	✖	✖	✖	✖	● (I/II)
alintegimod, ipilimumab, nivolumab	✖	✖	✖	✖	● (I/II)
atezolizumab, pelareorep	✖	✖	✖	✖	● (I/II)
BR-790, tislelizumab	✖	✖	✖	✖	● (I/II)
celecoxib, toripalimab	✖	✖	✖	✖	● (I/II)
chemotherapy, KSQ-004, aldesleukin	✖	✖	✖	✖	● (I/II)
chemotherapy, leucovorin, pembrolizumab	✖	✖	✖	✖	● (I/II)
denileukin diftitox, pembrolizumab	✖	✖	✖	✖	● (I/II)
EU-101	✖	✖	✖	✖	● (I/II)
IDE-275	✖	✖	✖	✖	● (I/II)
INBRX-106, pembrolizumab	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

Microsatellite instability-High (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
invikafusp alfa (Marengo Therapeutics)	✖	✖	✖	✖	● (I/II)
MDNA-11, pembrolizumab	✖	✖	✖	✖	● (I/II)
NDI-219216	✖	✖	✖	✖	● (I/II)
NEO-212, pembrolizumab, nivolumab	✖	✖	✖	✖	● (I/II)
NP-G2-044, anti-PD-1	✖	✖	✖	✖	● (I/II)
PRJ1-3024	✖	✖	✖	✖	● (I/II)
spartalizumab, pazopanib	✖	✖	✖	✖	● (I/II)
ST-067, obinutuzumab	✖	✖	✖	✖	● (I/II)
ST-316, fruquintinib, bevacizumab, chemotherapy	✖	✖	✖	✖	● (I/II)
toripalimab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (I/II)
TT-702, anti-PD-1	✖	✖	✖	✖	● (I/II)
vusolimogene oderparepvec, nivolumab	✖	✖	✖	✖	● (I/II)
ABSK-043	✖	✖	✖	✖	● (I)
ATX-559	✖	✖	✖	✖	● (I)
CS-23546	✖	✖	✖	✖	● (I)
CVL-006	✖	✖	✖	✖	● (I)
HRO-761, tislelizumab, chemotherapy, pembrolizumab	✖	✖	✖	✖	● (I)
interferon alpha (Werewolf Therapeutics), pembrolizumab	✖	✖	✖	✖	● (I)
NWY-001	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, ABBV-CLS-484, VEGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, natural killer cell therapy	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, umbilical cord blood NK cells	✖	✖	✖	✖	● (I)
pembrolizumab, KFA115	✖	✖	✖	✖	● (I)
RO-7589831	✖	✖	✖	✖	● (I)
SG-001	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

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	✖	✖	✖	●	✖
nivolumab	✖	✖	✖	○	● (III)
anti-PD-1	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
nivolumab + relatlimab	✖	✖	✖	○	✖
pembrolizumab	✖	✖	✖	○	✖
cetuximab, binimetinib, encorafenib	✖	✖	✖	✖	● (II/III)
bevacizumab, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, chemotherapy, leucovorin	✖	✖	✖	✖	● (II)
cetuximab, encorafenib	✖	✖	✖	✖	● (II)
cetuximab, panitumumab, encorafenib, antimalarial	✖	✖	✖	✖	● (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, vemurafenib, chemotherapy	✖	✖	✖	✖	● (II)
encorafenib, cetuximab, chemotherapy	✖	✖	✖	✖	● (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)

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
LOH percentage	***9.88%***
BARD1	***LOH, 2q35(215593375-215674382)x2***
FANCL	***LOH, 2p16.1(58386886-58468467)x2***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 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. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
3. 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
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
7. 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
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
10. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
11. 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
12. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
13. 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
14. 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
15. 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
16. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
17. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
18. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
19. 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
20. 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
21. 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
22. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
23. Yoshida et al. Microsatellite instability-high is rare events in refractory pediatric solid tumors. Pediatr Hematol Oncol. 2022 Aug;39(5):468-474. PMID: 34964684
24. Klein et al. Vascular wall-resident CD44+ multipotent stem cells give rise to pericytes and smooth muscle cells and contribute to new vessel maturation. PLoS One. 2011;6(5):e20540. PMID: 21637782
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
27. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
28. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2025]
29. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2025]
30. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
31. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 3.2025]
32. NCCN Guidelines® - NCCN-Hepatocellular Carcinoma [Version 1.2025]

References (continued)

33. NCCN Guidelines® - NCCN-Biliary Tract Cancers [Version 1.2025]
34. NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2025]
35. NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2025]
36. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
37. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
38. 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
39. 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
40. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
41. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
42. Malynn et al. A20: A multifunctional tool for regulating immunity and preventing disease. Cell Immunol. 2019 Jun;340:103914. PMID: 31030956
43. Giordano et al. The tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) imposes a brake on antitumor activity of CD8 T cells. Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):11115-20. PMID: 25024217
44. Küppers. The biology of Hodgkin's lymphoma. Nat Rev Cancer. 2009 Jan;9(1):15-27. PMID: 19078975
45. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
46. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
47. 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
48. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
49. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
50. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
51. 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
52. 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
53. 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
54. 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
55. 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
56. 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
57. 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
58. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation
59. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167
60. 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
61. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165

References (continued)

62. 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
63. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
64. 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
65. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
66. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]
67. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]
68. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 3.2024]
69. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]
70. 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
71. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. Front Immunol. 2020;11:569358. PMID: 33117357
72. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. Pharmacol Res. 2016 Jun;108:75-79. PMID: 27149915
73. 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
74. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. Genes Dev. 2013 Apr 15;27(8):819-35. PMID: 23630073
75. 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
76. 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
77. 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
78. 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
79. 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
80. 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
81. 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
82. 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
83. Tiacci et al. BRAF mutations in hairy-cell leukemia. N. Engl. J. Med. 2011 Jun 16;364(24):2305-15. PMID: 21663470
84. 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
85. 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
86. 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
87. 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
88. 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
89. 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

References (continued)

90. 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
91. 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
92. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
93. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/202806s038,217514s009lbl.pdf
94. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210496s018lbl.pdf
95. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
96. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204114s038,217513s009lbl.pdf
97. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210498s011lbl.pdf
98. Subbiah et al. Clinical Development of BRAF plus MEK Inhibitor Combinations. Trends Cancer. 2020 Sep;6(9):797-810. PMID: 32540454
99. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
100. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761034s053lbl.pdf
101. https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html
102. 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
103. https://biomed-valley.com/news/#press-releases
104. https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food
105. 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/
106. 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
107. 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
108. 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
109. 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
110. 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
111. 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
112. 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
113. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov. 2014 Jan;4(1):80-93. PMID: 24265155
114. Froimchuk et al. Histone H3 lysine 4 methyltransferase KMT2D. Gene. 2017 Sep 5;627:337-342. PMID: 28669924
115. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. Front Cell Neurosci. 2014;8:349. PMID: 25389387
116. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene. 2006 Mar 13;25(11):1659-72. PMID: 16550166
117. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. Br J Cancer. 2020 Apr;122(9):1277-1287. PMID: 32047295
118. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. Mol Carcinog. 2014 Apr;53(4):314-24. PMID: 23143693
119. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. Oncotarget. 2017 Jan 10;8(2):3640-3648. PMID: 27690298

References (continued)

120. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. PLoS One. 2015;10(5):e0127524. PMID: 26010150

121. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573