

Patient Name: 김현진
Gender: Female
Sample ID: N26-4

Primary Tumor Site: Ovary
Collection Date: 2025.12.15

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	BRAF p.(D594G) c.1781A>G	NTRK1	None detected
BRCA1	BRCA1 deletion	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	6.64 Mut/Mb measured
Genomic Instability	GIM 2 (Low)

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

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	AKT1 p.(E17K) c.49G>A AKT serine/threonine kinase 1 Allele Frequency: 63.56% Locus: chr14:105246551 Transcript: NM_001014431.2	None*	capivasertib + hormone therapy ^{1, 2 / II} +	5
IIC	BRAF p.(D594G) c.1781A>G B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 46.70% Locus: chr7:140453154 Transcript: NM_004333.6	None*	None*	6

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	ARID1A p.(E1935Rfs*21) c.5803delG	None*	None*	1
	AT-rich interaction domain 1A			
	Allele Frequency: 53.61%			
	Locus: chr1:27106190			
	Transcript: NM_006015.6			
IIC	BRCA1 deletion	None*	None*	1
	BRCA1, DNA repair associated			
	Locus: chr17:41197602			

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources
BRIP1 deletion, CDK12 deletion, Microsatellite stable, NF1 c.6704+1G>A, RAD51C deletion, RAD51D deletion, TP53 p.(E294*) c.880G>T, MPL amplification, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, LARP4B p.(S599Ffs*10) c.1795_1796insT, NQO1 p.(P187S) c.559C>T, USP9X deletion, DDX3X deletion, ZMYM3 deletion, PHF6 deletion, Tumor Mutational Burden, Genomic Instability (Low)

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
AKT1	p.(E17K)	c.49G>A	COSM33765	chr14:105246551	63.56%	NM_001014431.2	missense
BRAF	p.(D594G)	c.1781A>G	COSM467	chr7:140453154	46.70%	NM_004333.6	missense
ARID1A	p.(E1935Rfs*21)	c.5803delG	.	chr1:27106190	53.61%	NM_006015.6	frameshift Deletion
NF1	p.(?)	c.6704+1G>A	.	chr17:29664899	36.53%	NM_001042492.3	unknown
TP53	p.(E294*)	c.880G>T	.	chr17:7577058	33.60%	NM_000546.6	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	40.79%	NM_000463.3	missense
LARP4B	p.(S599Ffs*10)	c.1795_1796insT	.	chr10:860910	4.74%	NM_015155.3	frameshift Insertion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	47.67%	NM_000903.3	missense
DOCK3	p.(?)	c.2002-1G>A	.	chr3:51274920	26.49%	NM_004947.5	unknown
DCHS2	p.(S752C)	c.2254A>T	.	chr4:155287584	4.58%	NM_001358235.2	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	73.40%	NM_002439.5	nonframeshift Insertion
CPVL	p.(W419R)	c.1255T>A	.	chr7:29070258	79.30%	NM_019029.3	missense
C8orf89	p.(I57S)	c.170T>G	.	chr8:74169319	67.13%	NM_001243237.1	missense
SMARCB1	p.(D172E)	c.516C>G	.	chr22:24145497	50.53%	NM_003073.5	missense

Variant Details (continued)

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
BRCA1	chr17:41197602	1	0.77
BRIP1	chr17:59760627	1	0.76
CDK12	chr17:37618286	1	0.73
RAD51C	chr17:56769933	1	0.82
RAD51D	chr17:33427950	1	0.8
MPL	chr1:43803495	5.17	1.84
HLA-A	chr6:29910229	0.38	0.57
USP9X	chrX:40982869	0.83	0.69
DDX3X	chrX:41193501	0.79	0.68
ZMYM3	chrX:70460753	0.81	0.69
PHF6	chrX:133511628	0.79	0.68
GNA13	chr17:63010302	0.87	0.7
H3-3B	chr17:73772413	0.62	0.64

Biomarker Descriptions

AKT1 p.(E17K) c.49G>A

AKT serine/threonine kinase 1

Background: The AKT1 gene encodes Protein Kinase B, a serine/threonine kinase, that belongs to a family of closely related protein kinases that also includes AKT2 and AKT3. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism^{112,113}.

Alterations and prevalence: AKT1 encodes a proto-oncogene that is the target of recurrent somatic mutations in cancer¹¹⁴. The most common recurrent mutation is E17K, which is located in the N-terminal pleckstrin homology (PH) domain. E17K is a gain-of-function activating mutation that constitutively targets AKT1 to the plasma membrane and leads to downstream signaling^{115,116}. Other recurrent activating mutations include L52H, Q79K, and D323Y/G/N, which disrupt negative regulatory interactions between the PH domain and the kinase domain¹¹⁷. AKT1 mutations in cancer are common in breast and endometrial cancers, where they occur at a prevalence of 2-5%⁴. AKT1 mutations are observed at a prevalence of 1-2% in bladder, colorectal, melanoma, and thyroid cancers^{4,5}. AKT1 is overexpressed via gene amplification in ovarian cancer, lung squamous cell cancer, and sarcoma at a prevalence of 2-5%^{4,5}.

Potential relevance: Currently no therapies are approved for AKT1 aberrations. However, in the phase II NCI-MATCH trial, the pan-AKT inhibitor capivasertib (AZD5363) demonstrated a partial response in 23% (8/35) of AKT1 E17K mutated solid tumor patients¹¹⁸. Results from a phase I clinical trial of capivasertib demonstrated partial responses in 9/52 heavily pre-treated patients with AKT1 E17K mutated solid tumors, with a median progression-free survival (PFS) of 5.5 months in ER positive breast cancer, 6.6 months in gynecologic cancers, and 4.2 months in other solid tumors¹¹⁹. In the same phase I study, an ovarian cancer patient with an AKT1 Q79K mutation demonstrated stable disease lasting 14 months¹¹⁹.

BRAF p.(D594G) c.1781A>G

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)¹³². 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^{133,134}. BRAF mutations are categorized into three distinct functional classes, namely, class 1, 2, and 3, and are defined

Biomarker Descriptions (continued)

by the dependency on the RAS pathway¹³⁵. 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 BRAF¹³⁵. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead^{135,136,137}.

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^{4,5}. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types^{136,138}. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions¹³⁶. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I¹³⁶. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms^{139,140,141}. 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 loop¹³⁸. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme^{4,5}. 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^{142,143,144,145,146}. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation^{137,142,144}. 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 gliomas¹⁴⁷. 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)^{4,5}. 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)^{4,5}.

Potential relevance: Vemurafenib¹⁴⁸ (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 insensitive¹³⁶. BRAF kinase inhibitors including dabrafenib¹⁴⁹ (2013) and encorafenib¹⁵⁰ (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib¹⁵⁰ is approved in combination with cetuximab¹⁵¹ (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 alterations¹³⁶. The MEK inhibitors, trametinib¹⁵² (2013) and binimetinib¹⁵³ (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 NSCLC¹⁵⁴. The combinations of dabrafenib/trametinib¹⁵² (2015) and vemurafenib/cobimetinib¹⁵⁵ (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 mutation¹⁴⁹. The PD-L1 antibody, atezolizumab¹⁵⁶, 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-1310¹⁵⁷ for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib¹⁵⁸ was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib¹⁵⁹ 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-2787¹⁶⁰, 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)¹⁶¹, 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 melanoma¹⁶². 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)^{163,164,165,166,167,168,169}. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported¹⁴⁶.

ARID1A p.(E1935Rfs*21) c.5803delG

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein¹. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes ARID1B^{1,46}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex^{46,47}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B⁴⁷. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{47,48}. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription⁴⁶. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function⁴⁶.

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors⁴⁸. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations⁴⁶. Somatic mutations in ARID1A have been identified in several cancers including 50% of ovarian clear cell carcinoma,

Biomarker Descriptions (continued)

30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma^{4,5,47}. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response⁴⁹. Biallelic deletion of ARID1A is observed in 3% of cholangiocarcinoma and stomach adenocarcinoma, and 2% of pheochromocytoma and paraganglioma^{4,5}. Alterations in ARID1A are also observed in pediatric cancers⁵. Somatic mutations in ARID1A are observed in 12% of non-Hodgkin lymphoma (2 in 17 cases), 8% of Hodgkin lymphoma (5 in 61 cases), 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of embryonal tumors (5 in 332 cases), 1% of glioma (4 in 297 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and peripheral nervous system tumors (2 in 1158 cases)⁵. Biallelic deletion of ARID1A is observed in 2% of peripheral nervous system cancers (2 in 91 cases), 1% of leukemia (3 in 250 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁵.

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800⁵⁰, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulumimostat⁵¹, dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{14,15}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{14,15}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{16,17,18}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{16,19}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{20,21,22,23,24,25,26,27}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{4,5}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)²⁸. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{29,30}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib³¹ (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, olaparib³¹ 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. Rucaparib³² is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib³³ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib³³ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA1. Niraparib³⁴ (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. Niraparib in combination with abiraterone acetate³⁵ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib³⁶ received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported³⁷. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality³⁸. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

Biomarker Descriptions (continued)

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA⁸⁵. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control⁸⁶. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{68,82}. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)⁸⁷. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer^{87,88}. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer^{85,89}.

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma^{4,5}.

Potential relevance: The PARP inhibitor, olaparib³¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy^{82,90}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability^{65,66,67}. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes^{65,66,67,68,69}. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype^{67,68}. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors⁶⁹. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene⁶⁹.

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma^{1,4}. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma^{1,4}.

Potential relevance: The PARP inhibitor, olaparib³¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib³³ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors^{68,69}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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 genome¹⁷⁰. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{171,172}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2¹⁷³. 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 D17S250¹⁷⁴. 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)¹⁷⁴. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{175,176,177,178,179}. 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 genes¹⁷². LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{171,172,176,180}.

Biomarker Descriptions (continued)

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^{171,172,181,182}. 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^{181,182}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁸³ (2014) and nivolumab¹⁸⁴ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁸³ 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 indication¹⁸³. Dostarlimab¹⁸⁵ (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^{177,186}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹⁸⁷ (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^{177,188,189}. 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 patients¹⁸⁹. 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^{190,191}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{190,191}.

NF1 c.6704+1G>A

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family⁶. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state^{6,7}. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival⁶. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)^{6,8,9}.

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements⁶. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis^{6,10}. Somatic mutations in NF1 are observed in several cancer types including 17% of skin cutaneous melanoma, 14% of uterine corpus endometrial carcinoma, and 12% of glioblastoma multiforme, lung adenocarcinoma, and lung squamous cell carcinoma^{4,5}. Structural variants in NF1 are observed in 3% of cholangiocarcinoma^{4,5}. Biallelic deletion of NF1 is observed in 6% of ovarian serous cystadenocarcinoma, 4% of sarcoma, and 2% of uterine corpus endometrial carcinoma, pheochromocytoma and paraganglioma, lung squamous cell carcinoma, adrenocortical carcinoma, glioblastoma multiforme, uterine carcinosarcoma, and acute myeloid leukemia^{4,5}. Alterations in NF1 are also observed in pediatric cancers⁵. Somatic mutations in NF1 are observed in 8% of soft tissue sarcoma (3 in 38 cases), 4% of B-lymphoblastic leukemia/lymphoma (9 in 252 cases), 3% of Hodgkin lymphoma (2 in 61 cases), 2% of glioma (6 in 297 cases), 1% of bone cancer (4 in 327 cases) and leukemia (4 in 354 cases), and less than 1% of peripheral nervous system tumors (7 in 1158 cases), embryonal tumors (2 in 332 cases), and Wilms tumor (1 in 710 cases)⁵. Biallelic deletion of NF1 is observed in 2% of bone cancer (1 in 42 cases) and less than 1% of leukemia (2 in 250 cases), Wilms tumor (1 in 136 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)⁵.

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)¹¹.

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs⁷⁶. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)⁷⁷. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)⁷⁸. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing⁷⁹. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity^{80,81}. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{68,82}.

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers⁴.

Potential relevance: The PARP inhibitor, olaparib³¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib³³ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation⁸³. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51D deletion

RAD51D paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁷⁷. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁷⁸. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁷⁹. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{68,82}. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer⁸⁴.

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer⁴.

Potential relevance: The PARP inhibitor, olaparib³¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors⁸². In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

TP53 p.(E294*) c.880G>T

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 repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis⁹¹. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential⁹². Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{93,94}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{4,5,95,96,97,98}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282^{4,5}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{99,100,101,102}. Alterations in TP53 are also observed in pediatric cancers^{4,5}. 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)^{4,5}. 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)^{4,5}.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁰³ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{104,105}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma¹⁰⁶. 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)^{9,55,107,108,109}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹¹⁰. 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 system¹¹¹.

Biomarker Descriptions (continued)

MPL amplification

MPL proto-oncogene, thrombopoietin receptor

Background: The MPL gene encodes the MPL proto-oncogene, a transmembrane thrombopoietin receptor. Binding of the cytokine thrombopoietin to MPL leads to JAK2 activation and subsequent signaling that regulates stem cell homeostasis, cell survival, and proliferation⁵². Mutations in MPL typically disrupt normal auto-inhibitory functions and result in subsequent ligand-independent thrombopoietin receptor activation⁵². Gain-of-function mutations in MPL are associated with myeloproliferative neoplasms (MPN) and hereditary thrombocytosis. Loss-of-function mutations are linked to bone marrow failure syndromes, due to the regulation of thrombopoiesis by thrombopoietin⁵³.

Alterations and prevalence: Somatic mutations in MPL are present in 3-5% of primary myelofibrosis (PMF)^{52,54}. Specifically, MPL W515L/K mutations are reported in 5-8% of myelofibrosis (MF) and 1-4% of essential thrombocythemia (ET)⁵⁵. Other observed MPL mutations include V501A, Y252H, and S204P⁵².

Potential relevance: MPL W515K/L mutations confer intermediate prognosis in MPN⁵⁵.

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^{1,58}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{58,59}. 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 resistance⁶⁰. 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^{60,61,62,63}. 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-38⁶⁴.

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^{4,5}.

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹. 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 cells⁷⁰. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁷¹. 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^{72,73,74}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁷⁵.

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma^{4,5}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{4,5}.

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

LARP4B p.(S599Fs*10) c.1795_1796insT

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein¹. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7². Along with LARP4, LARP4B is part of the LARP4 family and is

Biomarker Descriptions (continued)

observed to bind AU-rich regions in the 3' untranslated regions of mRNAs². In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B³.

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma^{4,5}. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma^{4,5}.

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-linked protein¹. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases¹². DUBs catalyze the removal of ubiquitin from target proteins, thereby counter-regulating post-translational ubiquitin modifications within the cell^{12,13}. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X¹³. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its substrates¹³. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair¹³.

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma^{4,5}. Biallelic deletion in USP9X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma^{4,5}. Alterations in USP9X are also observed in the pediatric population⁵. Somatic mutations are observed in 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (1 in 311 cases)⁵. Biallelic deletion in USP9X is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁵.

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

DDX3X deletion

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II^{1,120}. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)^{120,121,122,123}. In DEAD-box proteins, the DEAD domain interacts with β - and γ -phosphates of ATP through Mg²⁺ and is required for ATP hydrolysis¹²⁰. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation^{124,125,126,127,128,129,130,131}. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance¹²⁴.

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma^{4,5}. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma^{4,5}.

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein¹. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)⁵⁶.

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical

Biomarker Descriptions (continued)

squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma, and 2% of thymoma, diffuse large B-cell lymphoma, head and neck squamous cell carcinoma, stomach adenocarcinoma, prostate adenocarcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, and breast invasive carcinoma^{4,5}. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African-American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively⁵⁷. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe^{4,5}. Alterations in ZMYM3 are also observed in pediatric cancers⁵. Somatic mutations in ZMYM3 are observed in 2% of embryonal tumors (8 in 332 cases), 1% of bone cancer (4 in 327 cases), and less than 1% of glioma (1 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)⁵.

Potential relevance: Currently, no therapies are approved for ZMYM3 aberrations.

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression^{40,41}.

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression^{40,42,43,44}. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)^{42,44}. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6⁴². PHF6 mutations are frequently observed in hematologic malignancies from male patients^{40,42}.

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy⁴⁵.

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

BRAF p.(D594G) c.1781A>G

exarafenib

Cancer type: Melanoma

Variant class: BRAF Class III

Supporting Statement:

The FDA has granted Fast Track designation to the pan-RAF inhibitor, KIN-2787, for the treatment of BRAF Class II or III alteration-positive and/or NRAS mutation-positive stage IIb to IV malignant melanoma that is metastatic or unresectable.

Reference:

<https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food>

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, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, 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, ERF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed (continued)

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSP02, RSP03, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, 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, ERRF1, 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, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types ☒ No evidence

AKT1 p.(E17K) c.49G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib + fulvestrant	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
ipatasertib + chemotherapy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (II)
ipatasertib, chemotherapy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (II)
HTL-0039732, atezolizumab	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (I/II)
ATV-1601	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (I)
IPN-60090, capivasertib	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (I)

BRAF p.(D594G) c.1781A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutemetinib, defactinib	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (II)
BPI-442096	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (I)
exarafenib, binimetinib	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (I)
JAB-3312	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (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.(D594G) c.1781A>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
PF-07799544, PF-07799933	×	×	×	×	● (I)
PF-07799933, cetuximab, binimetinib	×	×	×	×	● (I)

ARID1A p.(E1935Rfs*21) c.5803delG

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	×	×	×	×	● (II)

BRCA1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	×	×	×	×	● (II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	7.5%
BRCA1	CNV, CN:1.0
BRCA1	LOH, 17q21.31(41197602-41276231)x1
BRIP1	CNV, CN:1.0
BRIP1	LOH, 17q23.2(59760627-59938976)x1
CDK12	CNV, CN:1.0
CDK12	LOH, 17q12(37618286-37687611)x1
RAD51B	LOH, 14q24.1(68290164-69061406)x3
RAD51C	CNV, CN:1.0
RAD51C	LOH, 17q22(56769933-56811619)x1
RAD51D	CNV, CN:1.0
RAD51D	LOH, 17q12(33427950-33446720)x1

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.2.4 data version 2025.12(007)). 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 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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. Seetharaman et al. The RNA-binding protein LARP4 regulates cancer cell migration and invasion. *Cytoskeleton (Hoboken)*. 2016 Nov;73(11):680-690. PMID: 27615744
3. Koso et al. Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma. *Cancer Res.* 2016 Apr 15;76(8):2254-64. PMID: 26933087
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
5. 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
6. Philpott et al. The NF1 somatic mutational landscape in sporadic human cancers. 2017 Jun 21;11(1):13. doi: 10.1186/s40246-017-0109-3. PMID: 28637487
7. Scheffzek et al. The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. *Science.* 1997 Jul 18;277(5324):333-8. PMID: 9219684
8. Fioretos et al. Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. *Blood.* 1999 Jul 1;94(1):225-32. PMID: 10381517
9. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
10. Brems et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. *Lancet Oncol.* 2009 May;10(5):508-15. PMID: 19410195
11. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
12. Dufner et al. Ubiquitin-specific protease 8 (USP8/UBPy): a prototypic multidomain deubiquitinating enzyme with pleiotropic functions. *Biochem Soc Trans.* 2019 Dec 20;47(6):1867-1879. PMID: 31845722
13. Lu et al. USP9X stabilizes BRCA1 and confers resistance to DNA-damaging agents in human cancer cells. *Cancer Med.* 2019 Nov;8(15):6730-6740. PMID: 31512408
14. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553
15. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene.* 2002 Dec 16;21(58):8981-93. PMID: 12483514
16. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA.* 2017 Jun 20;317(23):2402-2416. PMID: 28632866
17. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 2007 Dec 5;99(23):1811-4. PMID: 18042939
18. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer.* 2007 Jan 15;96(1):11-5. PMID: 17213823
19. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr.* 2020 Aug;4(4):pkaa029. PMID: 32676552
20. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews®* [Internet]. PMID: 20301425
21. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin. Proc.* 2010 Dec;85(12):1111-20. PMID: 21123638
22. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Nov 1;108(44):18032-7. PMID: 22006311
23. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J. Clin. Oncol.* 2012 Jul 20;30(21):2654-63. PMID: 22711857
24. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol. Biomarkers Prev.* 2004 Dec;13(12):2078-83. PMID: 15598764
25. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003 Oct 24;302(5645):643-6. PMID: 14576434
26. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer.* 2000 Nov;83(10):1301-8. PMID: 11044354
27. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environ Mol Mutagen.* 2022 Jul;63(6):308-316. PMID: 36054589

References (continued)

28. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br. J. Cancer*. 2018 Nov;119(11):1401-1409. PMID: 30353044
29. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005 Apr 14;434(7035):913-7. PMID: 15829966
30. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005 Apr 14;434(7035):917-21. PMID: 15829967
31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
35. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
36. <https://www.jnj.com/media-center/press-releases/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-niraparib-for-the-treatment-of-metastatic-castration-resistant-prostate-cancer>
37. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J. Pathol*. 2013 Feb;229(3):422-9. PMID: 23165508
38. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.)*. 2018 Nov;71:172-176. PMID: 30177437
39. <https://www.senhwabio.com/en/news/20220125>
40. Wendorff et al. Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL. *Cancer Discov*. 2019 Mar;9(3):436-451. PMID: 30567843
41. Lower et al. Mutations in PHF6 are associated with Börjeson-Forssman-Lehmann syndrome. *Nat. Genet*. 2002 Dec;32(4):661-5. PMID: 12415272
42. Van Vlierberghe et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. *Nat. Genet*. 2010 Apr;42(4):338-42. PMID: 20228800
43. Van Vlierberghe et al. PHF6 mutations in adult acute myeloid leukemia. *Leukemia*. 2011 Jan;25(1):130-4. PMID: 21030981
44. Yoo et al. Somatic mutation of PHF6 gene in T-cell acute lymphoblastic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. *Acta Oncol*. 2012 Jan;51(1):107-11. PMID: 21736506
45. Patel et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N. Engl. J. Med*. 2012 Mar 22;366(12):1079-89. PMID: 22417203
46. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. *Cancer Discov*. 2013 Jan;3(1):35-43. PMID: 23208470
47. Wilson et al. SWI/SNF nucleosome remodellers and cancer. *Nat. Rev. Cancer*. 2011 Jun 9;11(7):481-92. PMID: 21654818
48. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. *Nat Commun*. 8;14648. PMID: 28262751
49. Mehrvarz Sarshekeh et al. ARID1A Mutation May Define an Immunologically Active Subgroup in Patients with Microsatellite Stable Colorectal Cancer. *Clin Cancer Res*. 2021 Mar 15;27(6):1663-1670. PMID: 33414133
50. <https://nuvectis.com/press-release-view/?i=114174>
51. <https://www.morphosys.com/en/news/morphosys-receives-us-fda-fast-track-designation-tulmimetostat-endometrial-cancer>
52. Kim et al. CALR, JAK2, and MPL mutation profiles in patients with four different subtypes of myeloproliferative neoplasms: primary myelofibrosis, essential thrombocythemia, polycythemia vera, and myeloproliferative neoplasm, unclassifiable. *Am. J. Clin. Pathol*. 2015 May;143(5):635-44. PMID: 25873496
53. Cleyrat et al. Gene editing rescue of a novel MPL mutant associated with congenital amegakaryocytic thrombocytopenia. *Blood Adv*. 2017 Sep 26;1(21):1815-1826. PMID: 29296828
54. Rozovski et al. An accurate, simple prognostic model consisting of age, JAK2, CALR, and MPL mutation status for patients with primary myelofibrosis. *Haematologica*. 2017 Jan;102(1):79-84. PMID: 27686378
55. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
56. Leung et al. ZMYM3 regulates BRCA1 localization at damaged chromatin to promote DNA repair. *Genes Dev*. 2017 Feb 1;31(3):260-274. PMID: 28242625
57. Liu et al. Distinct Genomic Alterations in Prostate Tumors Derived from African American Men. *Mol Cancer Res*. 2020 Dec;18(12):1815-1824. PMID: 33115829

References (continued)

58. 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
59. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene.* 2006 Mar 13;25(11):1659-72. PMID: 16550166
60. 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
61. 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
62. 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
63. 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
64. Karas et al. *JCO Oncol Pract.* 2021 Dec 3:OP2100624. PMID: 34860573
65. Malgorzata et al. CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. *Nat Commun.* 2019 Apr 15;10(1):1757. PMID: 30988284
66. Joshi et al. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. *J. Biol. Chem.* 2014 Mar 28;289(13):9247-53. PMID: 24554720
67. Blazek et al. The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.* 2011 Oct 15;25(20):2158-72. PMID: 22012619
68. Lord et al. BRCAness revisited. *Nat. Rev. Cancer.* 2016 Feb;16(2):110-20. PMID: 26775620
69. Paculová et al. The emerging roles of CDK12 in tumorigenesis. doi: 10.1186/s13008-017-0033-x. eCollection 2017. PMID: 29090014
70. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
71. 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
72. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
73. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
74. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
75. 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
76. Somyajit et al. RAD51C: a novel cancer susceptibility gene is linked to Fanconi anemia and breast cancer. *Carcinogenesis.* 2010 Dec;31(12):2031-8. PMID: 20952512
77. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. *Genes (Basel).* 2018 Dec 13;9(12). PMID: 30551670
78. 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
79. 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
80. Badie et al. RAD51C facilitates checkpoint signaling by promoting CHK2 phosphorylation. *J. Cell Biol.* 2009 May 18;185(4):587-600. PMID: 19451272
81. Renglin Lindh et al. RAD51C (RAD51L2) is involved in maintaining centrosome number in mitosis. *Cytogenet. Genome Res.* 2007;116(1-2):38-45. PMID: 17268176
82. 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
83. Min et al. RAD51C-deficient cancer cells are highly sensitive to the PARP inhibitor olaparib. *Mol. Cancer Ther.* 2013 Jun;12(6):865-77. PMID: 23512992
84. Godin et al. Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication. *Biochem. Cell Biol.* 2016 Oct;94(5):407-418. PMID: 27224545

References (continued)

85. Ali et al. BRIP-1 germline mutation and its role in colon cancer: presentation of two case reports and review of literature. *BMC Med Genet.* 2019 May 7;20(1):75. PMID: 31064327
86. Daino et al. Loss of the BRCA1-interacting helicase BRIP1 results in abnormal mammary acinar morphogenesis. *PLoS ONE.* 2013;8(9):e74013. PMID: 24040146
87. Taniguchi et al. Molecular pathogenesis of Fanconi anemia: recent progress. *Blood.* 2006 Jun 1;107(11):4223-33. PMID: 16493006
88. Weber-Lassalle et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. *Breast Cancer Res.* 2018 Jan 24;20(1):7. PMID: 29368626
89. Ramus et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J. Natl. Cancer Inst.* 2015 Nov;107(11). PMID: 26315354
90. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin. Cancer Res.* 2014 Feb 1;20(3):764-75. PMID: 24240112
91. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013 Jul;27(4):254-71. PMID: 23885265
92. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell.* 2014 Mar 17;25(3):304-17. PMID: 24651012
93. 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
94. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med.* 2017 Apr 3;7(4). PMID: 28270529
95. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25. PMID: 22960745
96. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
97. 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
98. 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
99. 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
100. 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
101. 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
102. 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
103. <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>
104. 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
105. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165
106. 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
107. 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
108. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
109. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
110. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
111. 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

References (continued)

112. Gonzalez et al. The Akt kinases: isoform specificity in metabolism and cancer. *Cell Cycle*. 2009 Aug 15;8(16):2502-8. PMID: 19597332
113. Porta et al. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front Oncol*. 2014 Apr 14;4:64. doi: 10.3389/fonc.2014.00064. eCollection 2014. PMID: 24782981
114. Mundi et al. AKT in cancer: new molecular insights and advances in drug development. *Br J Clin Pharmacol*. 2016 Oct;82(4):943-56. PMID: 27232857
115. Carpten et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*. 2007 Jul 26;448(7152):439-44. Epub 2007 Jul 4. PMID: 17611497
116. Shoji et al. The oncogenic mutation in the pleckstrin homology domain of AKT1 in endometrial carcinomas. *Br. J. Cancer*. 2009 Jul 7;101(1):145-8. PMID: 19491896
117. Parikh et al. Disruption of PH-kinase domain interactions leads to oncogenic activation of AKT in human cancers. *Proc. Natl. Acad. Sci. U.S.A.* 2012 Nov 20;109(47):19368-73. PMID: 23134728
118. American Association for Cancer Research. Capivasertib Active against AKT1-Mutated Cancers. *Cancer Discov*. 2018 Nov 14. PMID: 30429128
119. Hyman et al. AKT Inhibition in Solid Tumors With AKT1 Mutations. *J. Clin. Oncol*. 2017 Jul 10;35(20):2251-2259. PMID: 28489509
120. Rocak et al. DEAD-box proteins: the driving forces behind RNA metabolism. *Nat Rev Mol Cell Biol*. 2004 Mar;5(3):232-41. PMID: 14991003
121. Fuller-Pace. The DEAD box proteins DDX5 (p68) and DDX17 (p72): multi-tasking transcriptional regulators. *Biochim Biophys Acta*. 2013 Aug;1829(8):756-63. PMID: 23523990
122. Ali. DEAD-box RNA helicases: The driving forces behind RNA metabolism at the crossroad of viral replication and antiviral innate immunity. *Virus Res*. 2021 Apr 15;296:198352. PMID: 33640359
123. Linder et al. Looking back on the birth of DEAD-box RNA helicases. *Biochim Biophys Acta*. 2013 Aug;1829(8):750-5. PMID: 23542735
124. Lin. DDX3X Multifunctionally Modulates Tumor Progression and Serves as a Prognostic Indicator to Predict Cancer Outcomes. *Int J Mol Sci*. 2019 Dec 31;21(1). PMID: 31906196
125. Song et al. The mechanism of RNA duplex recognition and unwinding by DEAD-box helicase DDX3X. *Nat Commun*. 2019 Jul 12;10(1):3085. PMID: 31300642
126. Zhou et al. Comprehensive proteomic analysis of the human spliceosome. *Nature*. 2002 Sep 12;419(6903):182-5. PMID: 12226669
127. Yedavalli et al. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. *Cell*. 2004 Oct 29;119(3):381-92. PMID: 15507209
128. Chao et al. DDX3, a DEAD box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21waf1/cip1 promoter, is a candidate tumor suppressor. *Cancer Res*. 2006 Jul 1;66(13):6579-88. PMID: 16818630
129. Chuang et al. Requirement of the DEAD-Box protein ded1p for messenger RNA translation. *Science*. 1997 Mar 7;275(5305):1468-71. PMID: 9045610
130. Shih et al. Candidate tumor suppressor DDX3 RNA helicase specifically represses cap-dependent translation by acting as an eIF4E inhibitory protein. *Oncogene*. 2008 Jan 24;27(5):700-14. PMID: 17667941
131. Lee et al. Human DDX3 functions in translation and interacts with the translation initiation factor eIF3. *Nucleic Acids Res*. 2008 Aug;36(14):4708-18. PMID: 18628297
132. 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
133. 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
134. 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
135. 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
136. 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
137. 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

References (continued)

138. 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
139. Tiacci et al. BRAF mutations in hairy-cell leukemia. *N. Engl. J. Med.* 2011 Jun 16;364(24):2305-15. PMID: 21663470
140. 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
141. 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
142. 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
143. 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
144. 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
145. 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
146. 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
147. 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
148. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
149. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/202806s038,217514s009lbl.pdf
150. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210496s018lbl.pdf
151. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
152. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204114s038,217513s009lbl.pdf
153. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210498s011lbl.pdf
154. Subbiah et al. Clinical Development of BRAF plus MEK Inhibitor Combinations. *Trends Cancer.* 2020 Sep;6(9):797-810. PMID: 32540454
155. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
156. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761034s058lbl.pdf
157. <https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html>
158. <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>
159. <https://biomed-valley.com/news/#press-releases>
160. <https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food>
161. <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/>
162. 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
163. 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
164. 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
165. Rzos 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
166. 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
167. Van Allen 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

References (continued)

168. 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
169. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov.* 2014 Jan;4(1):80-93. PMID: 24265155
170. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
171. 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
172. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
173. 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
174. 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
175. 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
176. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
177. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
178. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
179. 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
180. 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
181. 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
182. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
183. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
184. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
185. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
186. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
187. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
188. 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
189. 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
190. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
191. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031