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Patient Name: 함복식
Gender: M
Sample ID: N25-219

Primary Tumor Site: skin
Collection Date: 2023.11.22

Sample Cancer Type: Melanoma

Report Highlights
5 Relevant Biomarkers
0 Therapies Available
8 Clinical Trials

Relevant Melanoma Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK2	None detected
KIT	***KIT amplification, KIT p.(Y578H) c.1732T>C***	NTRK3	None detected
NRAS	None detected	RET	None detected
NTRK1	None detected	ROS1	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***5.69 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CDK4 amplification* cyclin dependent kinase 4 Locus: chr12:58142242	None*	None*	5
IIC	*KIT amplification* KIT proto-oncogene receptor tyrosine kinase Locus: chr4:55589693	None*	None*	4
IIC	*FLT4 amplification* fms related tyrosine kinase 4 Locus: chr5:180030092	None*	None*	3
IIC	*KDR amplification* kinase insert domain receptor Locus: chr4:55955541	None*	None*	3
IIC	*PDGFRA amplification* platelet derived growth factor receptor alpha Locus: chr4:55131078	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.

Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.06(006). The content of this report has not been evaluated or approved by the FDA, EMA or other regulatory agencies.

Prevalent cancer biomarkers without relevant evidence based on included data sources

KIT p.(Y578H) c.1732T>C, MDM2 amplification, Microsatellite stable, PTPN11 amplification, RICTOR amplification, HLA-A p.(L180) c.539T>A, HDAC9 p.(A625Qfs*19) c.1872delA, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KIT	p.(Y578H)	c.1732T>C	.	chr4:55593666	91.33%	NM_000222.3	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	37.89%	NM_001242758.1	nonsense
HDAC9	p.(A625Qfs*19)	c.1872delA	.	chr7:18767342	5.08%	NM_178425.3	frameshift Deletion
ST6GAL2	p.(?)	c.944-1G>T	.	chr2:107450603	3.19%	NM_032528.3	unknown
KIT	p.(H630D)	c.1888C>G	.	chr4:55594185	94.34%	NM_000222.3	missense
FBXW7	p.(S148T)	c.443G>C	.	chr4:153332513	35.94%	NM_033632.3	missense
HLA-B	p.(I90K)	c.269_270delTCinsAG	.	chr6:31324538	100.00%	NM_005514.8	missense
MYO5A	p.(R1226H)	c.3677G>A	.	chr15:52643623	2.94%	NM_000259.3	missense
FANCI	p.(V191M)	c.571G>A	.	chr15:89807159	71.01%	NM_001113378.2	missense
AMER1	p.(A229P)	c.685G>C	.	chrX:63412482	100.00%	NM_152424.4	missense
STAG2	p.(L464F)	c.1392G>T	.	chrX:123191803	39.08%	NM_001042749.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDK4	chr12:58142242	59.31	20.48
KIT	chr4:55589693	41.15	14.31
FLT4	chr5:180030092	4.68	1.91
KDR	chr4:55955541	42.34	14.71
PDGFRA	chr4:55131078	48.12	16.68
MDM2	chr12:69202958	105.94	36.34
PTPN11	chr12:112856771	55.78	19.29
RICTOR	chr5:38942342	5.37	2.14
MAP3K1	chr5:56111388	5.29	2.12

Biomarker Descriptions

CDK4 amplification

cyclin dependent kinase 4

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[108,109]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma

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Biomarker Descriptions (continued)

protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[110]. Germline mutations in CDK4 are associated with familial melanoma[111,112,113].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[114,115,116]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[8,9,117,118].

Potential relevance: Currently, no therapies are approved for CDK4 aberrations. Amplification of region 12q14-15, which includes CDK4, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/welldifferentiated liposarcoma (ALT/WDLS)[48]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015), abemaciclib (2017), and ribociclib (2017), are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

KIT amplification, KIT p.(Y578H) c.1732T>C

KIT proto-oncogene receptor tyrosine kinase

Background: The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[14,15]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[16]. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, promoting cell proliferation and survival[17].

Alterations and prevalence: Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels). Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity[18]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[19]. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers[9,18,19]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[20,21].

Potential relevance: Imatinib[22] (2001) is approved for KIT positive unresectable or metastatic GIST and adult patients with aggressive systemic mastocytosis (SM) who do not have the D816V c-Kit mutation or whose c-Kit mutational status is unknown. Imatinib is also recommended for activating mutations, including KIT P577_W582delinsPYD and KIT V560D in melanoma and exon 9 and 11 sensitizing mutations in GIST[23,24,25,26]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[27]. Additionally, detection of activating mutations in KIT is useful as an ancillary technique in the diagnosis of GIST[25]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[28]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[29,30].

FLT4 amplification

fms related tyrosine kinase 4

Background: The FLT4 gene encodes the fms related receptor tyrosine kinase 4, also known as VEGFR3[1]. FLT4 is a type 2 transmembrane cell surface receptor tyrosine kinase (RTK) and is a member of a family of cognate RTKs called vascular endothelial growth factor receptors (VEGFRs) that also includes VEGFR1 (FLT-1) and VEGFR2 (KDR)[10,11]. Ligand binding to FLT4, including by VEGF-C and VEGF-D, results in FLT4 activation and has been observed to promote tumor metastasis through lymphangiogenesis[10,71].

Alterations and prevalence: Somatic mutations in FLT4 are observed in 12% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 6% of colorectal adenocarcinoma and stomach adenocarcinoma, 5% of kidney chromophobe, 4% of lung squamous cell carcinoma and lung adenocarcinoma, and 3% of cervical squamous cell carcinoma, pancreatic adenocarcinoma, adrenocortical carcinoma, and bladder urothelial carcinoma[8,9]. Amplifications are observed in 7% of kidney renal clear cell carcinoma and adrenocortical carcinoma, 4% of uterine carcinosarcoma, and 3% of sarcoma[8,9].

Potential relevance: Currently, no therapies are approved for FLT4 aberrations. Although not approved for specific FLT4 aberrations, the tyrosine kinase inhibitor, sorafenib, is a potent inhibitor of FLT4 and has been approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment[72,73].

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Biomarker Descriptions (continued)

KDR amplification

kinase insert domain receptor

Background: The KDR gene encodes the kinase insert domain receptor protein, also known as the vascular endothelial growth factor receptor 2 (VEGFR2). KDR is a type 2 transmembrane cell surface receptor tyrosine kinase (RTK) and is a member of a family of cognate RTKs called VEGFRs that also includes VEGFR1 (FLT-1) and VEGFR3[10,11]. KDR binds to ligands VEGF-A, VEGF-C, VEGF-D, and VEGF-E and is the principal mediator of VEGF-induced angiogenic signaling[10,11]. Upon ligand stimulation, KDR undergoes dimerization and trans-autophosphorylation, leading to activation of the RAF-MEK-ERK and PI3K-AKT pathways, promoting endothelial cell proliferation and migration[11,12].

Alterations and prevalence: Somatic mutations in KDR are observed in 14% of melanoma, 8% of lung adenocarcinoma, uterine carcinoma, and diffuse large B-cell lymphoma (DLBCL)[8,9]. Amplifications are observed in 6% of glioblastoma multiforme (GBM)[8,9]. Overexpression of KDR has been observed in various cancer types including mammary, colorectal, non-small cell lung, and urothelial carcinomas[12].

Potential relevance: Currently, no therapies are approved for KDR aberrations. Drugs targeting KDR reduce angiogenesis or lymphangiogenesis and typically competitively bind to the ATP-site of KDR[11]. Drugs that may target KDR include FDA approved inhibitors apatinib, axitinib, nintedanib, sorafenib, sunitinib, ramucirumab, and pazopanib, although there are no known alterations associated with these approved therapies. FDA approved monoclonal antibodies targeting the KDR pathway include bevacizumab that binds to the ligand VEGF-A and prevents the interaction with KDR[11,13].

PDGFRA amplification

platelet derived growth factor receptor alpha

Background: The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT[14,15]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[74]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[75]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12, and all 3 tyrosine kinases are often co-amplified in cancer[76]. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, which promotes cell proliferation and survival[77].

Alterations and prevalence: Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall[78,79,80,81]. PDGFRA recurrent mutations are also observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of lung adenocarcinoma, 5% of colorectal adenocarcinoma, 4% of lung squamous cell carcinoma, glioblastoma multiforme, and bladder urothelial carcinoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% of cervical squamous cell carcinoma, liver hepatocellular carcinoma, brain lower grade glioma, and ovarian serous cystadenocarcinoma[8,9]. PDGFRA amplification is observed in 13% of glioblastoma multiforme, 5% of lung squamous cell carcinoma, 4% of brain lower grade glioma, 3% of sarcoma and skin cutaneous melanoma, and 2% of esophageal adenocarcinoma, testicular germ cell tumors, lung adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[8,9]. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1::PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome[82,83,84]. Alterations of PDGFRA are rare in pediatric cancers[8,9]. Somatic mutations are observed in 2% of glioma, and less than 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), and leukemia (1 in 354 cases)[8,9]. PDGFRA is amplified in 5% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases)[8,9].

Potential relevance: Avapritinib[85] (2020) is a tyrosine kinase inhibitor (TKI) that is approved by the FDA for metastatic or unresectable gastrointestinal stromal tumors (GISTs) harboring PDGFRA exon 18 mutations, including PDGFRA D842V mutation. The FDA has granted fast track designation to crenolanib[86] (2017) for harboring PDGFRA D842V mutation. Imatinib[22] (2001) is a TKI approved for patients diagnosed with chronic eosinophilic leukemia harboring the FIP1L1::PDGFRA fusion. Additionally, imatinib is recommended for the treatment of GISTs harboring PDGFRA exon 18 mutations, with the exception of D842V[25]. Amplification of PDGFRA is a diagnostic marker of H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma[87,88]. PDGFRA rearrangements are associated with poor risk in pediatric acute lymphoblastic leukemia[89,90].

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING

Biomarker Descriptions (continued)

domain[43]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[43]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[44]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[44]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[44].

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma[8,9]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[45]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[46,47].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[48].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[49]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[50,51]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[52]. 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[53]. 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)[53]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[54,55,56,57,58]. 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[51]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[50,51,55,59].

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[50,51,60,61]. 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[60,61].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[62] (2014) and nivolumab[63] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[62] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[62]. Dostarlimab[64] (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[56,65]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[66] (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[56,67,68]. 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[68]. 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[69,70]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[69,70].

PTPN11 amplification

protein tyrosine phosphatase, non-receptor type 11

Background: The PTPN11 gene encodes a tyrosine phosphatase non-receptor type 11 protein, and is also known as Src homology region 2 domain-containing phosphatase-2 (SHP-2)[31]. PTPN11 is a member of the protein tyrosine phosphatase (PTP) family that is ubiquitously expressed and regulates cellular growth, differentiation, mitotic cycle, and oncogenic transformation. PTPN11 contains two tandem N-terminal Src homology-2 domains (N-SH2 and C-SH2), a PTP catalytic domain, and uncharacterized C-terminal domain[32]. PTPN11 regulates various signaling processes including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, and JAK/STAT pathways[33,34]. Germline mutations in PTPN11 are associated with LEOPARD syndrome and Noonan syndrome with a predisposition to juvenile myelomonocytic leukemia (JMML) or myeloproliferative neoplasms (MPN)[35,36]. Somatic mutations in PTPN11 are associated with JMML[37,38] and solid tumors such as lung, colon, and thyroid[32,39]

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Biomarker Descriptions (continued)

Alterations and prevalence: Somatic alterations in PTPN11 include mutations and amplification[35,40]. PTPN11 mutations occur in 6% of uterine carcinoma and 5% of acute myeloid leukemia (AML) cases[9]. Mutations including E76K and D61Y result in PTPN11 activation and are associated with 30% of JMML[34].

Potential relevance: Currently, no therapies are approved for PTPN11 aberrations. Somatic mutations in PTPN11 confer drug resistance to venetoclax and azacitidine in AML[41,42].

RICTOR amplification

RPTOR independent companion of MTOR complex 2

Background: The RICTOR gene encodes the RPTOR independent companion of MTOR complex 2, a core component of the mTOR complex-2 (mTORC2)[1,98]. RICTOR complexes with MTOR, DEPTOR, mSin1 and Protor1/2 to form the mTORC2 complex, which regulates cell proliferation and survival by phosphorylating members of the PKA/PKG/PKC family of protein kinases[99]. The mTORC2 complex is a downstream effector of the PI3K/AKT/MTOR signaling pathway and facilitates integration of the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK signaling pathways[100,101,102]. Independent of mTORC2, RICTOR can interact with integrin-linked kinases and promote phosphorylation of AKT[99,103]. Aberrations in RICTOR can lead to downstream pathway activation promoting cell proliferation and survival, supporting an oncogenic role for RICTOR[104].

Alterations and prevalence: Amplification of RICTOR is observed in several types of solid tumors and has been observed to correlate with protein overexpression[105]. Specifically, RICTOR amplification is observed in 10% of lung squamous cell carcinoma, 8% of esophageal adenocarcinoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% of adrenocortical carcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, ovarian serous cystadenocarcinoma, and sarcoma[8,9]. Somatic mutations in RICTOR are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, 5% of stomach adenocarcinoma and bladder urothelial carcinoma, and 3% of lung adenocarcinoma and lung squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for RICTOR aberrations. RICTOR overexpression is associated with poor survival in hepatocellular carcinoma and endometrial carcinoma[106,107].

HLA-A p.(L180*) c.539T>A

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.

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

histone deacetylase 9

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[1]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[91]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[91,92]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[91]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[91,93].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell

Biomarker Descriptions (continued)

lymphoma (CTCL) following treatment with two systemic therapies[94]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[95]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[96]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[97].

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,

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Genes Assayed (continued)

Genes Assayed with Full Exon Coverage (continued)

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

CDK4 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
PF-07220060, midazolam	✖	✖	✖	✖	● (I/II)

KIT amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)
NB003	✖	✖	✖	✖	● (I)

FLT4 amplification

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

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

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Relevant Therapy Summary (continued)

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

KDR amplification

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

PDGFRA amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✖	✖	✖	✖	● (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	***10.45%***
Not Detected	***Not Applicable***

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.

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