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Patient Name: 고수복
Gender: Male
Sample ID: N26-15

Primary Tumor Site: duodenum
Collection Date: 2025.12.26

Sample Cancer Type: Liposarcoma

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Relevant Liposarcoma Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
CDK4	***CDK4 amplification***	NTRK2	None detected
GLI1	None detected	NTRK3	None detected
MDM2	***MDM2 amplification***	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***2.84 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*CDK4 amplification* cyclin dependent kinase 4 Locus: chr12:58142242 **Diagnostic significance:** Dedifferentiated Liposarcoma	None*	None*	6
IA	*MDM2 amplification* MDM2 proto-oncogene Locus: chr12:69202958 **Diagnostic significance:** Dedifferentiated Liposarcoma	None*	None*	5

*** 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

ESR1 amplification, MAPK1 amplification, NF1 p.(Q2228) c.6682C>T, UGT1A1 p.(G71R) c.211G>A, HLA-B deletion, CARD11 amplification, RAC1 amplification, NQO1 p.(P187S) c.559C>T, RPS6KB1 amplification, GNA13 amplification, H3-3B amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NF1	p.(Q2228*)	c.6682C>T	.	chr17:29664876	67.46%	NM_001042492.3	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	49.17%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.55%	NM_000903.3	missense
MAML3	p.(Q488_Q494delinsHDS)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACACGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	40.00%	NM_018717.5	nonframeshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	59.47%	NM_018717.5	frameshift Block Substitution
FAT1	p.(I1967M)	c.5901T>G	.	chr4:187541839	47.72%	NM_005245.4	missense
KMT2C	p.(H330N)	c.988C>A	.	chr7:151970814	8.60%	NM_170606.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDK4	chr12:58142242	88.7	31.78
MDM2	chr12:69202958	109.7	39.23
ESR1	chr6:152163831	11.08	4.23
MAPK1	chr22:22123473	4.79	1.99
HLA-B	chr6:31322252	0.93	0.62
CARD11	chr7:2949684	9.97	3.83
RAC1	chr7:6426823	7.24	2.86
RPS6KB1	chr17:57970507	5.89	2.38
GNA13	chr17:63010302	5.54	2.25
H3-3B	chr17:73772413	4.86	2.01
TNFAIP3	chr6:138192315	7.8	3.06
PMS2	chr7:6012922	6.45	2.58
HDAC9	chr7:18201905	10.04	3.85
TBX3	chr12:115109599	34.03	12.37
RNF43	chr17:56432226	5.51	2.24
PPM1D	chr17:58677747	5.79	2.35
AXIN2	chr17:63526027	5.73	2.33
PRKAR1A	chr17:66511464	5.76	2.33

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
SOX9	chr17:70117435	5.76	2.33

Biomarker Descriptions

CDK4 amplification

cyclin dependent kinase 4

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6[1,82]. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[83,84]. CDK4 is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[85]. Germline mutations in CDK4 are associated with familial melanoma[86,87,88]. Overexpression of CDK4 has been observed in several cancers including epithelial cancers of endocrine tissues and mucosa, melanoma, breast cancer, gliomas, and leukemia[89].

Alterations and prevalence: Recurrent somatic mutations of CDK4 are observed in 3% of skin cutaneous melanoma and 2% of uterine corpus endometrial carcinoma[8,9]. Somatic mutations at codons K22 and R24, which are essential for binding and inhibition by p16/CDKN2A, are associated with melanoma formation and metastasis.[90,91,92,93]. CDK4 is recurrently amplified in 18% of sarcoma, 7% of adrenocortical carcinoma, 6% of cholangiocarcinoma, 5% of lung adenocarcinoma, 4% of brain lower grade glioma and skin cutaneous melanoma, and 2% of stomach adenocarcinoma, diffuse large B-cell lymphoma, and pancreatic adenocarcinoma[8,9,94,95]. Alterations in CDK4 are also observed in pediatric cancers[9]. Somatic mutations are observed in 2% of Hodgkin lymphoma[9]. CDK4 amplification is observed in 5% of bone cancer (2 in 42 cases), 2% of peripheral nervous system tumors (2 in 91 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[9].

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)[18]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015)[96], abemaciclib (2017)[97], and ribociclib (2017)[98], 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.

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene[1]. 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 domain[19]. 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[19]. 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[20]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[20]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[20].

Alterations and prevalence: MDM2 is amplified in 19% of sarcoma, 9% of bladder urothelial carcinoma, 8% of glioblastoma multiforme, 7% of adrenocortical carcinoma, 5% of uterine carcinosarcoma, lung adenocarcinoma, esophageal adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and ovarian serous cystadenocarcinoma, 3% of breast invasive carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, testicular germ cell tumors, and lung squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma[8,9]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[21]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[22,23]. Somatic mutations in MDM2 are observed in 2% of uterine corpus endometrial carcinoma, adrenocortical carcinoma, and sarcoma[8,9]. Alterations in MDM2 are also observed in pediatric cancers[9]. Amplification of MDM2 is observed in 2% of bone cancer (1 in 42 cases), 1% of Wilms tumor (2 in 136 cases) and peripheral nervous system tumors (1 in 91 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[9]. Somatic mutations in MDM2 are observed in 2% of non-Hodgkin lymphoma (1 in 17 cases) and less than 1% of bone cancer (3 in 327 cases) and embryonal tumors (1 in 332 cases)[9].

Biomarker Descriptions (continued)

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[18].

ESR1 amplification

estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses[1]. A related gene, ESR2, encodes the cognate ERβ protein[1]. ERα is a ligand-activated transcription factor regulated by the hormone estrogen[24,25]. Estrogen binding to ERα results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[26]. In neuroblastoma, MYCN-driven miR-17~92 cluster expression suppresses ESR1 to block differentiation, whereas estrogen-activated ESR1 cooperates with ETS-1 to promote MMP1/9 expression and tumor proliferation, migration, and invasion[27,28].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[29,30,31,32]. Somatic mutations in ESR1 are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of stomach adenocarcinoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, and esophageal adenocarcinoma[8,9]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[33,34,35,36,37]. Amplification of ESR1 is observed in 5% of uterine carcinosarcoma, 4% of sarcoma, 3% of uterine corpus endometrial carcinoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and breast invasive carcinoma[8,9]. Alterations in ESR1 are also observed in pediatric cancers[38]. Somatic mutations in ESR1 are observed in 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 1% of glioma (3 in 297 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), leukemia (1 in 311 cases), and peripheral nervous system cancers (1 in 1158 cases)[38]. Amplification of ESR1 is observed in less than 1% of leukemia (1 in 250 cases)[38].

Potential relevance: The FDA has approved elacestrant[39] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[40]. The FDA also approved imlunestrant[41] (2025) for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. The FDA has also granted fast track designations to the following therapies: AC-699[42] (2024) and lasofoxifene[43] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizestrant[44] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[45] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[46] (1977), fulvestrant[47] (2002), letrozole[48] (1995), and exemestane[49] (2005) are FDA approved for ER-positive metastatic breast cancers[50,51]. Although ERα and ERβ positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[52,53,54].

MAPK1 amplification

mitogen-activated protein kinase 1

Background: The MAPK1 gene encodes the mitogen-activated protein kinase 1, also known as ERK2[1]. MAPK1 is involved in the ERK1/2 signaling pathway along with MAPK3, MAP2K2, MAP2K4, BRAF, and RAF1[55,56]. Activation of MAPK proteins occurs through a kinase signaling cascade[56,57,58]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[56,57,58]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[56,57,58]. MAPK1 activation leads to homodimerization and phosphorylation of downstream targets including transcription factors RSK, MSK, and MYC, cytoskeletal molecules, and nucleoporins[59]. MAPK1 mutations have been observed to confer gain of function and promote MAPK pathway signaling, supporting an oncogenic role for MAPK1[60,61].

Alterations and prevalence: Somatic mutations in MAPK1 are observed in up to 4% of cervical squamous cell carcinoma, and up to 2% of head and neck squamous cell and uterine corpus endometrial carcinomas[8,9]. The most common missense mutations occur at codon 322[8,9]. Amplifications in MAPK1 are observed in up to 4% of sarcoma, and 3% of bladder carcinoma, lung squamous carcinoma, and ovarian cancer[8,9].

Potential relevance: Currently, no therapies are approved for MAPK1 aberrations.

Biomarker Descriptions (continued)

NF1 p.(Q2228*) c.6682C>T

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[13]. 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[13,14]. 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 survival[13]. 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)[13,15,16].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[13]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[13,17]. 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[8,9]. Structural variants in NF1 are observed in 3% of cholangiocarcioma[8,9]. 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[8,9]. Alterations in NF1 are also observed in pediatric cancers[9]. 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)[9]. 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)[9].

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)[18].

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[1,99]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[99,100]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[101]. 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[101,102,103,104]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[105].

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

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[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-B[7].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal

Biomarker Descriptions (continued)

adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[8,9]. Biallelic loss of HLA-B is observed in 5% of DLBCL[8,9].

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

CARD11 amplification

caspase recruitment domain family member 11

Background: The CARD11 gene encodes caspase recruitment domain family member 11 protein[1]. CARD11, also known as CARMA1, is a scaffold protein that functions in the adaptive immune system to mediate antigen-receptor signaling through the NF-κB, JNK, and MTOR signaling pathways[70,71,72]. In response to T- or B- cell receptor triggering, CARD11 is activated, which results in binding of various cofactors, including BCL10, MALT1, and RNF31[71]. Cofactor recruitment to CARD11 leads to the ubiquitination of BCL10, which then associates with the IκB (IKK) complex through the IKKγ subunit, thereby leading to IκB activation and downstream NF-κB signaling[71]. CARD11 gain-of-function mutations are associated with constitutive activation of NF-κB signaling and aberrant proliferation of diffuse large B-cell lymphoma (DLBCL), supporting an oncogenic role for CARD11[71].

Alterations and prevalence: Somatic mutations in CARD11 are observed in 17% of DLBCL, 14% of skin cutaneous melanoma, 10% of uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma and stomach adenocarcinoma, and 6% of lung adenocarcinoma[8,9]. Amplification of CARD11 is observed in 5% of esophageal adenocarcinoma, 4% of bladder urothelial carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3% of stomach adenocarcinoma, 2% of adrenocortical carcinoma, DLBCL, and skin cutaneous melanoma[8,9].

Potential relevance: Currently, no therapies are approved for CARD11 aberrations.

RAC1 amplification

ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)

Background: The RAC1 gene encodes Rac family small GTPase 1[1]. RAC1 is one of 23 members of the RHO subfamily of GTPases within the RAS superfamily[62,63,64]. The RAS superfamily includes the RHO, RAS, RAB, ARF, RHEB, and Gα subfamilies[62,63,64,65]. RHO subfamily members are known for the regulation of several pathways involved in cell morphology, motility, and proliferation[66,67,68]. RAC1 can exist in an inactive GDP-bound form as well as in an active GTP-bound form[64]. Guanine nucleotide exchange factors (GEFs) activate RAC1 by facilitating the release of GDP to allow for binding of GTP, while GTPase-activating proteins (GAPs) facilitate the reverse, that is converting GTP-bound RAC1 to an inactive state[64].

Alterations and prevalence: Somatic mutations in RAC1 are observed in 6% of skin cutaneous melanoma and 2% of uterine carcinosarcoma[8,9]. The P29S mutation is recurrent in melanoma and is potentially associated with resistance to BRAF inhibitors[8,9,69]. RAC1 is amplified in 6% of esophageal squamous cell carcinoma, 4% of uterine carcinosarcoma, bladder urothelial carcinoma, and sarcoma, as well as 2% of skin cutaneous melanoma and esophageal adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for RAC1 aberrations.

RPS6KB1 amplification

ribosomal protein S6 kinase B1

Background: The RPS6KB1 gene encodes ribosomal protein S6 kinase B1[1]. RPS6KB1, also known as S6K1, belongs to the AGC kinase family along with AKT, PKA, PKC, and PKG[78]. RPS6KB1 is a downstream target of mTORC1 phosphorylation which results in activation of RPS6KB1 and subsequent phosphorylation of the 40S ribosomal protein S6[79,80]. Aberrations including amplification and overexpression of RPS6KB1 have been associated with various cancer types including breast, kidney, and hepatocellular carcinoma, supporting an oncogenic role for RPS6KB1[79,81].

Alterations and prevalence: Somatic mutations in RPS6KB1 are observed in 2% uterine corpus endometrial carcinoma[8,9]. Amplification of RPS6KB1 is observed in 9% of breast invasive carcinoma, 5% of liver hepatocellular carcinoma and mesothelioma, and 4% uterine carcinosarcoma[8,9].

Potential relevance: Currently, no therapies are approved for RPS6KB1 aberrations.

Biomarker Descriptions (continued)

GNA13 amplification

G protein subunit alpha 13

Background: The GNA13 gene encodes the G protein subunit α 13. GNA13 functions as the α subunit of heterotrimeric G proteins, which are responsible for binding guanine nucleotide, hydrolyzing GTP, and interacting with specific receptor and effector molecules[10]. Specifically, GNA13 mediated signaling is observed to impact several cellular processes including the regulation of cell growth, transformation, cell adhesion, and migration[11]. GNA13 deregulation, including overexpression, has been observed to result in increased levels of chemokines which can promote cell proliferation[10]. In contrast, mutations in GNA13 leading to inactivation result in B-cell release from germinal centers of lymphoid tissues to peripheral blood and may promote lymphomagenesis in germinal center diffuse large B-cell and Burkitt's lymphomas[12].

Alterations and prevalence: Somatic mutations in GNA13 are observed in 5% of DLBCL, 4% of uterine and 3% of bladder cancer[8,9]. Homozygous deletions are observed in 6% of DLBCL[8,9]. GNA13 is the most frequently mutated gene in germinal center derived B-cell lymphomas, including 25% of Burkitt lymphoma[12]. The majority of such mutations are predicted to result in loss of protein function[12].

Potential relevance: Currently, no therapies are approved for GNA13 aberrations.

H3-3B amplification

H3.3 histone B

Background: The H3-3B gene encodes the H3.3 histone B protein, also known as H3F3B, a sequence variant member of the histone H3 family[1,73]. Specifically, H3-3B is expressed independently of DNA replication in non-dividing or terminally differentiated cells[74]. Histone H3, along with histones H4, H2A, and H2B form the nucleosome, which is a component of chromatin[75]. Histones play a role in transcriptional regulation, DNA repair, replication, and chromosomal stability[75]. Mutations in H3 have been observed to impact global histone methylation and gene transcription, which may promote tumorigenesis[76].

Alterations and prevalence: Somatic mutations in H3-3B are observed in 1% of bladder urothelial carcinoma, skin cutaneous melanoma, mesothelioma, and uterine corpus endometrial carcinoma[8,9]. H3-3B amplifications are observed in 4% of breast invasive carcinoma, uterine carcinosarcoma and liver hepatocellular carcinoma, 3% of mesothelioma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, esophageal adenocarcinoma and cervical squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for H3-3B aberrations. The FDA has granted fast track designation to ONC201 for the treatment of adult high-grade glioma harboring a H3 K27M mutation[77].

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,

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations (continued)

CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

CDK4 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
camrelizumab + dalpiciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

CDK4 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)

MDM2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
retifanlimab, pemigatinib	✖	✖	✖	✖	● (II)
alrizomadlin, toripalimab	✖	✖	✖	✖	● (I/II)
SA53-MDM2	✖	✖	✖	✖	● (I/II)
siremadlin, pazopanib	✖	✖	✖	✖	● (I/II)
BTX-A51	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***29.78%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
RAD54L	***LOH, 1p34.1(46714017-46743978)x3***

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 (6.2.4 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. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
10. Zhang et al. GNA13 promotes tumor growth and angiogenesis by upregulating CXC chemokines via the NF-κB signaling pathway in colorectal cancer cells. Cancer Med. 2018 Nov;7(11):5611-5620. PMID: 30267476
11. Worzfeld et al. G(12)/G(13)-mediated signalling in mammalian physiology and disease. Trends Pharmacol Sci. 2008 Nov;29(11):582-9. PMID: 18814923
12. Healy et al. GNA13 loss in germinal center B cells leads to impaired apoptosis and promotes lymphoma in vivo. Blood. 2016 Jun 2;127(22):2723-31. PMID: 26989201
13. 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
14. 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
15. 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
16. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
17. Brems et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol. 2009 May;10(5):508-15. PMID: 19410195
18. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
19. Toledo et al. MDM2 and MDM4: p53 regulators as targets in anticancer therapy. Int. J. Biochem. Cell Biol. 2007;39(7-8):1476-82. PMID: 17499002
20. Zhao et al. The regulation of MDM2 oncogene and its impact on human cancers. Acta Biochim. Biophys. Sin. (Shanghai). 2014 Mar;46(3):180-9. PMID: 24389645
21. Helei et al. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. Cancer Cell International volume 19, Article number: 216 (2019). PMID: 31440117
22. Dembla et al. Prevalence of MDM2 amplification and coalterations in 523 advanced cancer patients in the MD Anderson phase 1 clinic. Oncotarget. 2018 Sep 4;9(69):33232-33243. PMID: 30237864
23. Momand et al. The MDM2 gene amplification database. Nucleic Acids Res. 1998 Aug 1;26(15):3453-9. PMID: 9671804
24. Paterni et al. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014 Nov;90:13-29. PMID: 24971815
25. Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen receptors. Pharmacol. Rev. 2006 Dec;58(4):773-81. PMID: 17132854
26. Marino et al. Estrogen signaling multiple pathways to impact gene transcription. Curr. Genomics. 2006;7(8):497-508. PMID: 18369406
27. Lovén et al. MYCN-regulated microRNAs repress estrogen receptor-alpha (ESR1) expression and neuronal differentiation in human neuroblastoma. Proc Natl Acad Sci U S A. 2010 Jan 26;107(4):1553-8. PMID: 20080637
28. Cao et al. Estrogen receptor α enhances the transcriptional activity of ETS-1 and promotes the proliferation, migration and invasion of neuroblastoma cell in a ligand dependent manner. BMC Cancer. 2015 Jun 30;15:491. PMID: 26122040

References (continued)

29. Chang. Tamoxifen resistance in breast cancer. Biomol Ther (Seoul). 2012 May;20(3):256-67. PMID: 24130921
30. Toy et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat. Genet. 2013 Dec;45(12):1439-45. PMID: 24185512
31. Jeselsohn et al. Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor-Positive Breast Cancer. Clin. Cancer Res. 2014 Apr 1;20(7):1757-1767. PMID: 24398047
32. Robinson et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet. 2013 Dec;45(12):1446-51. doi: 10.1038/ng.2823. Epub 2013 Nov 3. PMID: 24185510
33. Hartmaier et al. Recurrent hyperactive ESR1 fusion proteins in endocrine therapy-resistant breast cancer. Ann. Oncol. 2018 Apr 1;29(4):872-880. PMID: 29360925
34. Matissek et al. Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor-Positive Breast Cancer. Cancer Discov. 2018 Mar;8(3):336-353. PMID: 29242214
35. Lei et al. ESR1 fusions drive endocrine therapy resistance and metastasis in breast cancer. Mol Cell Oncol. 2018;5(6):e1526005. PMID: 30525098
36. Lei et al. Functional Annotation of ESR1 Gene Fusions in Estrogen Receptor-Positive Breast Cancer. Cell Rep. 2018 Aug 7;24(6):1434-1444.e7. PMID: 30089255
37. Basudan et al. Frequent ESR1 and CDK Pathway Copy-Number Alterations in Metastatic Breast Cancer. Mol. Cancer Res. 2019 Feb;17(2):457-468. PMID: 30355675
38. De Braekeleer et al. ETV6 fusion genes in hematological malignancies: a review. Leuk. Res. 2012 Aug;36(8):945-61. PMID: 22578774
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639Orig1s001lbl.pdf
40. NCCN Guidelines® - NCCN-Breast Cancer [Version 5.2025]
41. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218881s000lbl.pdf
42. https://www.accutarbio.com/accutar-biotechnology-receives-fda-fast-track-designation-for-ac699-in-er-her2-breast-cancer/
43. https://sermonixpharma.com/sermonix-receives-fda-fast-track-designation-for-investigational-drug-lasofoxifene/
44. https://www.astrazeneca.com/content/dam/az/PDF/2022/h1-2022/H1-2022-results-announcement.pdf
45. https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/17970s37s44s49lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021344s044lbl.pdf
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020726s043lbl.pdf
49. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020753s025lbl.pdf
50. Tamoxifen--an update on current data and where it can now be used. Breast Cancer Res. Treat. 2002 Oct;75 Suppl 1:S7-12; discussion S33-5. PMID: 12353826
51. Kim et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. J. Clin. Oncol. 2011 Nov 1;29(31):4160-7. PMID: 21947828
52. Jeselsohn et al. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015 Oct;12(10):573-83. PMID: 26122181
53. Angus et al. ESR1 mutations: Moving towards guiding treatment decision-making in metastatic breast cancer patients. Cancer Treat. Rev. 2017 Jan;52:33-40. PMID: 27886589
54. Reinert et al. Clinical Implications of ESR1 Mutations in Hormone Receptor-Positive Advanced Breast Cancer. Front Oncol. 2017 Mar 15;7:26. PMID: 28361033
55. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011 Mar;75(1):50-83. PMID: 21372320
56. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. Clin. Cancer Res. 2013 May 1;19(9):2301-9. PMID: 23406774
57. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3). PMID: 32046099
58. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 2014 Jan;171(1):24-37. PMID: 24117156
59. Roskoski. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol. Res. 2012 Aug;66(2):105-43. PMID: 22569528

References (continued)

60. Roskoski. MEK1/2 dual-specificity protein kinases: structure and regulation. Biochem. Biophys. Res. Commun. 2012 Jan 6;417(1):5-10. PMID: 22177953
61. Marampon et al. Biological Rationale for Targeting MEK/ERK Pathways in Anti-Cancer Therapy and to Potentiate Tumour Responses to Radiation. Int J Mol Sci. 2019 May 23;20(10). PMID: 31126017
62. Bustelo et al. GTP-binding proteins of the Rho/Rac family: regulation, effectors and functions in vivo. Bioessays. 2007 Apr;29(4):356-70. PMID: 17373658
63. Bishop et al. Rho GTPases and their effector proteins. Biochem. J. 2000 Jun 1;348 Pt 2:241-55. PMID: 10816416
64. Bosco et al. Rac1 GTPase: a "Rac" of all trades. Cell. Mol. Life Sci. 2009 Feb;66(3):370-4. PMID: 19151919
65. Colicelli. Human RAS superfamily proteins and related GTPases. Sci. STKE. 2004 Sep 7;2004(250):RE13. PMID: 15367757
66. Sahai et al. Cross-talk between Ras and Rho signalling pathways in transformation favours proliferation and increased motility. EMBO J. 2001 Feb 15;20(4):755-66. PMID: 11179220
67. Zhou et al. Cell type-specific signaling function of RhoA GTPase: lessons from mouse gene targeting. J. Biol. Chem. 2013 Dec 20;288(51):36179-88. PMID: 24202176
68. Yoshioka et al. Overexpression of small GTP-binding protein RhoA promotes invasion of tumor cells. Cancer Res. 1999 Apr 15;59(8):2004-10. PMID: 10213513
69. Watson et al. The RAC1 P29S hotspot mutation in melanoma confers resistance to pharmacological inhibition of RAF. Cancer Res. 2014 Sep 1;74(17):4845-4852. PMID: 25056119
70. Rawlings et al. The CARMA1 signalosome links the signalling machinery of adaptive and innate immunity in lymphocytes. Nat Rev Immunol. 2006 Nov;6(11):799-812. PMID: 17063183
71. Wang et al. Coordinated regulation of scaffold opening and enzymatic activity during CARD11 signaling. J Biol Chem. 2019 Oct 4;294(40):14648-14660. PMID: 31391255
72. Bedsaul et al. Mechanisms of Regulated and Dysregulated CARD11 Signaling in Adaptive Immunity and Disease. Front Immunol. 2018;9:2105. PMID: 30283447
73. Draizen et al. HistoneDB 2.0: a histone database with variants--an integrated resource to explore histones and their variants. Database (Oxford). 2016;2016. PMID: 26989147
74. Frank et al. Differential expression of human replacement and cell cycle dependent H3 histone genes. Gene. 2003 Jul 17;312:135-43. PMID: 12909349
75. Audia et al. Histone Modifications and Cancer. Cold Spring Harb Perspect Biol. 2016 Apr 1;8(4):a019521. PMID: 27037415
76. Wan et al. Histone H3 Mutations in Cancer. Curr Pharmacol Rep. 2018;4(4):292-300. PMID: 30101054
77. https://www.chimerix.com/our-pipeline/
78. Tavares et al. The S6K protein family in health and disease. Life Sci. 2015 Jun 15;131:1-10. PMID: 25818187
79. Pópulo et al. The mTOR signalling pathway in human cancer. Int J Mol Sci. 2012;13(2):1886-918. PMID: 22408430
80. Mossmann et al. mTOR signalling and cellular metabolism are mutual determinants in cancer. Nat Rev Cancer. 2018 Dec;18(12):744-757. PMID: 30425336
81. Sinclair et al. The 17q23 amplicon and breast cancer. Breast Cancer Res Treat. 2003 Apr;78(3):313-22. PMID: 12755490
82. Rodríguez-Díez et al. Cdk4 and Cdk6 cooperate in counteracting the INK4 family of inhibitors during murine leukemogenesis. Blood. 2014 Oct 9;124(15):2380-90. PMID: 25157181
83. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
84. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov. 2016 Apr;6(4):353-67. PMID: 26658964
85. Weinberg. The retinoblastoma protein and cell cycle control. Cell. 1995 May 5;81(3):323-30. PMID: 7736585
86. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol. Cell. Biol. 2002 Jan;22(2):644-56. PMID: 11756559
87. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat. Genet. 1996 Jan;12(1):97-9. PMID: 8528263
88. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes Cancer. 2005 Sep;44(1):10-8. PMID: 15880589
89. Baker et al. CDK4: a master regulator of the cell cycle and its role in cancer. Genes Cancer. 2022;13:21-45. PMID: 36051751
90. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. Biochem. Biophys. Res. Commun. 1998 Aug 19;249(2):550-5. PMID: 9712735

References (continued)

91. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. Cancer Res. 1998 Jan 1;58(1):109-13. PMID: 9426066
92. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. Proc. Natl. Acad. Sci. U.S.A. 2001 Nov 6;98(23):13312-7. PMID: 11606789
93. Kollmann et al. The interplay of CDK4 and CDK6 in melanoma. Oncotarget. 2019 Feb 15;10(14):1346-1359. PMID: 30858922
94. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
95. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
96. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/207103s023lbl.pdf
97. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208716s019lbl.pdf
98. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209092s024lbl.pdf
99. 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
100. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene. 2006 Mar 13;25(11):1659-72. PMID: 16550166
101. 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
102. 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
103. 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
104. 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
105. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573