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

Patient Name: 박전규
Gender: M
Sample ID: N25-303

Primary Tumor Site:
Collection Date: 2025.10.27

Sample Cancer Type: Lung Cancer

Report Highlights

3 Relevant Biomarkers
0 Therapies Available
12 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***9.47 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CCNE1 amplification* cyclin E1 Locus: chr19:30303647	None*	None*	11
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC deletion, ARAF amplification, KEAP1 p.(Q563) c.1687C>T, MAP2K7 deletion, MSH3 deletion, PIK3R1 deletion, PMS2 deletion, RICTOR amplification, SLX4 p.(E1701*) c.5101G>T, TP53 p.(V157F) c.469G>T, TNFRSF14 deletion, NFE2L2 amplification, TET2 deletion, INPP4B deletion, TERT amplification, CTNND2 amplification, IL7R amplification, MAP3K1 deletion, RASA1 deletion, ERAP1 deletion, ADAMTS2 deletion, HDAC9 deletion, EIF1AX amplification, AR amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KEAP1	p.(Q563*)	c.1687C>T	.	chr19:10599889	87.53%	NM_203500.2	nonsense
SLX4	p.(E1701*)	c.5101G>T	.	chr16:3633150	84.70%	NM_032444.4	nonsense
TP53	p.(V157F)	c.469G>T	COSM10670	chr17:7578461	89.35%	NM_000546.6	missense
CDH10	p.(P223T)	c.667C>A	.	chr5:24535368	12.51%	NM_006727.5	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	57.21%	NM_002439.5	nonframeshift Insertion
HLA-C	p.([V319A;V320D])	c.956_959delTTGTinsCTGA	.	chr6:31237799	2.25%	NM_001243042.1	missense, missense
PSMB8	p.(D123H)	c.367G>C	.	chr6:32810489	61.16%	NM_148919.4	missense
MUC19	p.(S2083F)	c.6248C>T	.	chr12:40873002	45.72%	NM_173600.2	missense
CYLD	p.(R786Q)	c.2357G>A	.	chr16:50827472	89.86%	NM_001042355.2	missense
ZFHX3	p.(D914H)	c.2740G>C	.	chr16:72984844	92.51%	NM_006885.4	missense
RPTOR	p.(P429S)	c.1285C>T	.	chr17:78820345	22.30%	NM_020761.3	missense
KIAA1755	p.(C337*)	c.1011C>A	.	chr20:36869522	37.87%	NM_001029864.2	nonsense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CCNE1	chr19:30303647	5.05	1.61
RAD50	chr5:131892978	0.33	0.66
RB1	chr13:48877953	0	0.23
APC	chr5:112043374	0.25	0.65
ARAF	chrX:47422311	3.8	2.12
MAP2K7	chr19:7968792	0.48	0.7
MSH3	chr5:79950540	0.35	0.67
PIK3R1	chr5:67522468	0.2	0.64
PMS2	chr7:6012922	0.38	0.68
RICTOR	chr5:38942342	14.95	3.59
TNFRSF14	chr1:2488070	0.08	0.62
NFE2L2	chr2:178095457	7.13	2.03

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
TET2	chr4:106155068	0.43	0.68
INPP4B	chr4:142949914	0.45	0.69
TERT	chr5:1253783	12.35	3.07
CTNND2	chr5:10988230	12.55	3.11
IL7R	chr5:35857035	15.73	3.74
MAP3K1	chr5:56111388	0.35	0.67
RASA1	chr5:86564256	0.23	0.65
ERAP1	chr5:96112128	0.03	0.61
ADAMTS2	chr5:178549645	0	0.58
HDAC9	chr7:18201905	0.2	0.64
EIF1AX	chrX:20148599	4.22	2.29
AR	chrX:66766015	3.78	2.11
SDHA	chr5:218412	12.98	3.2
PRDM9	chr5:23509577	11.88	2.98
CDH10	chr5:24487706	13.43	3.28
ADAMTS12	chr5:33527235	14.6	3.52
PDGFRB	chr5:149497160	0.4	0.68
FGFR4	chr5:176517731	0.05	0.61
FLT4	chr5:180030092	0	0.55
FANCG	chr9:35074046	5.2	1.64
LATS2	chr13:21548922	5.03	1.6
YES1	chr18:724481	0.38	0.68
BCL2	chr18:60795830	0	0.4
ZRSR2	chrX:15808582	3.7	2.08
BCOR	chrX:39911340	4	2.2
USP9X	chrX:40982869	3.85	2.14
DDX3X	chrX:41193501	3.75	2.1
KDM6A	chrX:44732715	3.7	2.08
RBM10	chrX:47006798	3.73	2.09
KDM5C	chrX:53221892	4.2	2.28
SMC1A	chrX:53406966	4.18	2.27
AMER1	chrX:63409727	4.05	2.22
ZMYM3	chrX:70460753	3.95	2.18

Biomarker Descriptions

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2[90]. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2) which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein[90]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis[91,92,93]. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1[90,94].

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers[4]. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.[90,94,95].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[96], in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers[97,98,99].

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[110,111]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[111,112]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[112,113]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[112,113]. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[112,114]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[115,116]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[117].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[4,5]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[118].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[119]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[119]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[120].

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[34,35]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[36]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[34,35,37]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[38].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[5]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[5]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[39,40,41].

Biomarker Descriptions (continued)

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

APC deletion

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[64]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[65,66]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[64,67]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[68].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[4,5,69]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[70,71].

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

ARAF amplification

A-Raf proto-oncogene, serine/threonine kinase

Background: The A-Raf proto-oncogene serine/threonine kinase is member of the RAF family of serine/threonine protein kinases which also includes BRAF and RAF-1 (CRAF). Although germline mutations of both BRAF and RAF1 are associated with RASopathies, a group of medical genetic syndromes due to the dysregulation of RAS/RAF/MEK/ERK signaling during development, ARAF is not associated with these conditions[60].

Alterations and prevalence: Recurrent somatic mutations in ARAF are observed in about 1% of lung adenocarcinoma and in non-Langerhans histiocytic neoplasms[61,62,63]. The primary recurrent mutation in ARAF occurs at codon S214, which represents a phosphorylation site that negatively regulates RAS binding and RAF activation via binding of 14-3-3 proteins[63]. ARAF gene amplification is observed in diverse cancer types, including 4% of ovarian cancers[4,5].

Potential relevance: Currently, no therapies are approved for ARAF aberrations. One case study reported that a patient with lung adenocarcinoma harboring ARAF S214C responded to treatment with sorafenib and remained progression free for five years[63]. Patients with histiocytosis and ARAF activating mutations also responsed to sorafenib[61,62].

KEAP1 p.(Q563*) c.1687C>T

kelch like ECH associated protein 1

Background: The KEAP1 gene encodes the kelch like ECH associated protein 1, a tumor suppressor and a member of the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex[1,124]. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2[125]. Aberrations in KEAP1 can result in loss of function leading to accumulation of NFE2L2, thereby altering the transcription genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation[125,126,127].

Alterations and prevalence: Somatic mutations in KEAP1 are observed in 18% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, 4% of uterine corpus endometrial carcinoma and head and neck squamous cell carcinoma, 3% of esophageal adenocarcinoma, and 2% of stomach adenocarcinoma, skin cutaneous melanoma, adrenocortical carcinoma, and bladder cancer[5]. Alterations in KEAP1 are also observed in pediatric cancers[5]. Somatic mutations in KEAP1 are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases), and embryonal tumors (1 in 332 cases)[5]. Biallelic deletion of KEAP1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for KEAP1 aberrations.

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[1]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[72,73,74]. Activation of MAPK

Biomarker Descriptions (continued)

proteins occurs through a kinase signaling cascade[72,73,75]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[72,73,75]. 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[72,73,75].

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma[4,5]. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[9,10]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[9,10]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[11].

Alterations and prevalence: Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma[4,5]. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MSH3 aberrations.

PIK3R1 deletion

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[147]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[147]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[147]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[148,149]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[148,149,150,151]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[152]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[147].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[4]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[4].

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

PMS2 deletion

PMS1 homolog 2, mismatch repair system component

Background: The PMS2 gene encodes the PMS1 homolog 2 protein[1]. PMS2 is a tumor suppressor gene that heterodimerizes with MLH1 to form the MutLα complex[9]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process[1]. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[42]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[9,42]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[9]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[43]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[44,45,46]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[44,47]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[45,47,48,49].

Alterations and prevalence: Somatic mutations in PMS2 are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, and 4% of adrenocortical carcinoma[4,5]. Iterations in PMS2 are observed in pediatric cancers[4,5]. Somatic

Biomarker Descriptions (continued)

mutations are observed in 3% of soft tissue sarcoma, 2% of B-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[4,5].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[50]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[51,52]. PMS2 mutations are consistent with high grade in pediatric diffuse gliomas[53,54].

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)[1,100]. 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[101]. 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[102,103,104]. Independent of mTORC2, RICTOR can interact with integrin-linked kinases and promote phosphorylation of AKT[101,105]. Aberrations in RICTOR can lead to downstream pathway activation promoting cell proliferation and survival, supporting an oncogenic role for RICTOR[106].

Alterations and prevalence: Amplification of RICTOR is observed in several types of solid tumors and has been observed to correlate with protein overexpression[107]. 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[4,5]. 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[4,5].

Potential relevance: Currently, no therapies are approved for RICTOR aberrations. RICTOR overexpression is associated with poor survival in hepatocellular carcinoma and endometrial carcinoma[108,109].

SLX4 p.(E1701*) c.5101G>T

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit[1]. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases[121]. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair[121,122,123]. Specifically, SLX4 localizes at DSB sites and recruits and interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1[121,122,123]. Germline SLX4 mutations are associated with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition[122].

Alterations and prevalence: Recurrent somatic mutations in SLX4 are observed in 11% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of stomach adenocarcinoma, and 4% of bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for SLX4 aberrations.

TP53 p.(V157F) c.469G>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 repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[153]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[154]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[155,156].

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%)[4,5,157,158,159,160]. 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[161,162,163,164]. Alterations in TP53 are also

Biomarker Descriptions (continued)

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, PC14586[165] (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[166,167]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[168]. 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)[20,22,29,169,170]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[130]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[171].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[128]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[128]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[128,129]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[128]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[129].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[130]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[131,132].

NFE2L2 amplification

nuclear factor, erythroid 2 like 2

Background: The NFE2L2 gene encodes the nuclear factor, erythroid 2 like 2 transcription factor, a member of the basic leucine zipper protein family[1]. NFE2L2, also known as NRF2, is a proto-oncogene that activates transcription of genes with antioxidant response elements (ARE)[127]. NFE2L2 targets include genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation[125,127]. NFE2L2 is negatively regulated by KEAP1, a Cul3 adaptor protein, that ubiquitinates NFE2L2[125].

Alterations and prevalence: Recurrent somatic mutations in NFE2L2 are observed in 14% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, and 5% of head and neck squamous cell carcinoma[4,5]. Deletion of NFE2L2 exon 2 or exon 2 and 3 result in an isoform leading to the lack of the KEAP1 interacting domain, NFE2L2 stabilization, and expression of NFE2L2 targets such as HMOX1, G6PD, PDGFC, FGF2, and NQO1[127,172].

Potential relevance: Currently, no therapies are approved for NFE2L2 aberrations. The FDA has granted fast track designation (2022) to the mTORC 1/2 inhibitor, sapanisertib (CB-228)[173], for patients with NFE2L2 mutated, unresectable or metastatic squamous non-small cell lung cancer (NSCLC) who have received prior platinum-based chemotherapy and immune checkpoint inhibitor therapy.

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,15]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[16,17]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[16,17]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4

Biomarker Descriptions (continued)

protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[16,17]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[15,18,19].

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[20]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[18,21]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[4,5]. Alterations in TET2 are also observed in the pediatric population[5]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[5]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5].

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[22]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[23]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[24].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,174]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[175]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[176,177].

Alterations and prevalence: Somatic mutations in INPP4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, 3% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma, and 2% of cervical squamous cell carcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[4,5]. Biallelic loss of INPP4B is observed in 2% of bladder urothelial carcinoma, uterine carcinosarcoma, and brain lower grade glioma[4,5]. Amplification of INPP4B is observed in 3% of cholangiocarcinoma and esophageal adenocarcinoma, and 2% of sarcoma, stomach adenocarcinoma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for INPP4B aberrations.

TERT amplification

telomerase reverse transcriptase

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)[55]. TERT is repressed in most differentiated cells, resulting in telomerase silencing[55]. In cancer, telomerase reactivation is known to contribute to cellular immortalization[55,56]. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization[55]. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness[55].

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5]. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)[56]. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription[55]. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma[4,5]. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen[57]. Alterations in TERT are rare in pediatric cancers[4,5]. Somatic mutations are observed in less than 1% of B-

Biomarker Descriptions (continued)

lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)[4,5]. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma[58,59]. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy[57].

CTNND2 amplification

catenin delta 2

Background: The CTNND2 gene encodes catenin delta 2 protein[1]. CTNND2, also known as NPRAP and δ-catenin, belongs to the delta subfamily of the β-catenin superfamily along with CTNND1[12]. Due to its interaction with the cell junction protein, E-cadherin, CTNND2 overexpression has been observed to disrupt E-cadherin distribution and promote tumor growth[12,13,14]. Additionally, CTNND2 alteration, particularly overexpression, is observed in several cancer types, supporting an oncogenic role for CTNND2[12,13,14].

Alterations and prevalence: Somatic mutations in CTNND2 are observed in 14% of skin cutaneous melanoma, 11% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 9% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, and 6% of head and neck squamous cell carcinoma, and colorectal adenocarcinoma[4,5]. Amplification of CTNND2 is observed in 13% of lung squamous cell carcinoma, 10% of lung adenocarcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma, and 7% of ovarian serous cystadenocarcinoma, sarcoma, adrenocortical adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CTNND2 aberrations.

IL7R amplification

interleukin 7 receptor

Background: The IL7R gene encodes the interleukin 7 receptor[1]. IL7R is commonly expressed in immune cells and plays a critical role in the development and homeostasis of the immune system, including the regulation of cell development, survival, and differentiation of T-cells[25,26]. IL7R may also play a role in the development of B-cells by controlling downstream signaling pathways, including the JAK/PI3K/AKT pathways[26]. Mutations and other aberrations in IL7R result in a gain-of-function, thereby supporting its oncogenic role[27].

Alterations and prevalence: Somatic mutations in IL7R are observed in 13% of skin cutaneous melanoma, 6% of lung squamous cell carcinoma, and 4% of uterine corpus endometrial carcinoma, lung adenocarcinoma, and stomach adenocarcinoma[4,5]. Amplification of IL7R is observed in 10% of lung squamous cell carcinoma, 9% of lung adenocarcinoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of stomach adenocarcinoma, and 5% of cervical squamous cell carcinoma and ovarian serous cystadenocarcinoma[4,5]. Alterations in IL7R are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 5% of T-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma (1 in 38 cases), 2% of B- lymphoblastic leukemia/lymphoma (4 in 252 cases), and less than 1% of embryonal tumor (3 in 332 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[4,5,28]. Amplification of IL7R is observed in about 5% of pediatric bone cancer[4,5].

Potential relevance: Currently, no therapies are approved for IL7R aberrations. The Philadelphia-chromosome-like (Ph-like) phenotype of acute lymphoblastic leukemia (ALL) is associated with mutations in tyrosine kinase pathway genes, including IL7R[28,29,30]. Testing for these abnormalities at diagnosis may aid in risk stratification[29]. Notably, mutations in IL7R are associated with unfavorable-risk features in pediatric acute lymphoblastic leukemia[30,31].

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[72,73,75]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[72,73,75]. 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[72,73,75]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[76]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[76]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[76].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[4,5]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[76]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

RASA1 deletion

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1[1]. RASA1 is a member of the RasGAP family, which includes RASA2[32,33]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[32]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[32]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[32]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[32].

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma[4,5]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein[1]. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[77,78]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[77,79]. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis[77,80,81]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[77,82].

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERAP1 aberrations.

HDAC9 deletion

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)[83]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[83,84]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[83]. 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[83,85].

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, 4% of esophageal adenocarcinoma, 3% of esophageal adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and kidney chromophobe[4,5]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[5]. Alterations in HDAC9 are also observed in pediatric cancers[5]. Somatic mutations in HDAC9 are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone

Biomarker Descriptions (continued)

cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[5]. Biallelic deletion of HDAC9 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[86] (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies. The pan-HDAC inhibitor, romidepsin[87] (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy. The pan-HDAC inhibitor, belinostat[88] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[89] (2024), for the treatment of recurrent glioblastoma.

EIF1AX amplification

eukaryotic translation initiation factor 1A, X-linked

Background: The EIF1AX gene encodes the eukaryotic translation initiation factor 1A X-linked protein[1]. EIF1AX, also known as EIF1A, stimulates protein translation initiation by promoting the recruitment of the ternary complex (TC; tRNA-eIF2-GTP) to the 40S ribosomal subunit and facilitating the assembly of the 43S preinitiation complex (PIC)[2,3].

Alterations and prevalence: Somatic mutations in EIF1AX are observed in 13% of uveal melanoma, 3% of uterine corpus endometrial carcinoma, and 1% of thymoma and thyroid carcinoma[4,5]. Mutations, including X113_splice, have been observed to be recurrent in thyroid cancers and have been proposed to cooperate with RAS mutation to drive thyroid tumorigenesis[3,4,5,6,7] Amplification of EIF1AX is observed in 2% of sarcoma, and 1% of cervical squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for EIF1AX aberrations. EIF1AX mutations are considered a marker of low risk of distant metastasis of uveal melanoma[8].

AR amplification

androgen receptor

Background: The AR gene encodes the androgen receptor protein (AR), a ligand-activated transcription factor regulated by the binding of the hormones testosterone and dihydrotestosterone[133,134]. Hormone binding to AR results in receptor dimerization, nuclear translocation, and target gene transcription, thus activating the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR signaling pathways, which promote cell proliferation and survival[134,135,136].

Alterations and prevalence: Alterations in AR function can result from overexpression, gene amplification, or mutations. AR mutations, including L702H, W742C/L, H875Y, and T878A, are commonly observed in 10-30% of castration-resistant prostate cancer and result in decreased ligand specificity, allowing other nuclear hormones to activate AR[137]. Androgen receptor splice variants have been reported in castration resistant prostate cancer[138,139]. The androgen receptor splice variant 7 (AR-V7) is a result of aberrant mRNA splicing of AR exons 1-3 and a cryptic exon 3, resulting in the expression of a constitutively active protein[139].

Potential relevance: The FDA has granted fast track designation (2022) to the selective androgen receptor targeting agonist, enobosarm, for the treatment of patients with androgen AR-positive, estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer[140]. The FDA also granted fast track designation (2016) to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for AR-positive triple-negative breast cancer (TNBC) patients[141]. Androgen deprivation therapy (ADT) such as abiraterone[142] (2011) and enzalutamide[143] (2011) are FDA approved for use in locally advanced and metastatic prostate cancers. Other ADT therapies including leuprolide and bicalutamide are specifically recommended in AR+ unresectable metastatic salivary gland tumors[144]. Although many men initially respond to ADT, most will develop hormone resistance. Resistance to ADT is also associated with other aberrations of the AR gene including mutations within the ligand binding domain and gene amplification[137,145,146]. The androgen receptor splice variant, AR-V7, lacks the ligand binding domain, resulting in constitutive activation and is associated with resistance to androgen deprivation therapy (ADT) in advanced prostate cancer[138].

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

CCNE1 amplification

camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda

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,

Genes Assayed (continued)

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

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

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
APR-1051	✖	✖	✖	✖	● (I/II)
ARTS-021	✖	✖	✖	✖	● (I/II)
ECI-830, hormone therapy, ribociclib	✖	✖	✖	✖	● (I/II)
INX-315, hormone therapy	✖	✖	✖	✖	● (I/II)
WJB-001	✖	✖	✖	✖	● (I/II)
ETX-197, hormone therapy	✖	✖	✖	✖	● (I)
lunresertib, camonsertib, Debio-0123	✖	✖	✖	✖	● (I)
nedisertib, tuvusertib	✖	✖	✖	✖	● (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

CCNE1 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
NKT-3964	✖	✖	✖	✖	● (I)
NKT-5097	✖	✖	✖	✖	● (I)

RAD50 deletion

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

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)

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

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 2025.10(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 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. 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. Fekete et al. The eIF1A C-terminal domain promotes initiation complex assembly, scanning and AUG selection in vivo. EMBO J. 2005 Oct 19;24(20):3588-601. PMID: 16193068
3. Krishnamoorthy et al. EIF1AX and RAS Mutations Cooperate to Drive Thyroid Tumorigenesis through ATF4 and c-MYC. Cancer Discov. 2019 Feb;9(2):264-281. PMID: 30305285
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. Gargano et al. Characterization and Clinical Significance of EIF1AX Mutations and Co-Mutations in Cytologically Indeterminate Thyroid Nodules: A 5-Year Retrospective Analysis. Acta Med Acad. 2021 Apr;50(1):4-12. PMID: 34075760
7. Simões-Pereira et al. The role of EIF1AX in thyroid cancer tumourigenesis and progression. J Endocrinol Invest. 2019 Mar;42(3):313-318. PMID: 29968046
8. NCCN Guidelines® - NCCN-Uveal Melanoma [Version 1.2025]
9. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
10. Tamura et al. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. Int J Clin Oncol. 2019 Sep;24(9):999-1011. PMID: 31273487
11. Ikeda et al. Close correlation between mutations of E2F4 and hMSH3 genes in colorectal cancers with microsatellite instability. Cancer Res. 1998 Feb 15;58(4):594-8. PMID: 9485005
12. Lu et al. Hum Genet. 2016 Oct;135(10):1107-16. PMID: 27380241
13. Zeng et al. delta-Catenin promotes prostate cancer cell growth and progression by altering cell cycle and survival gene profiles. Mol Cancer. 2009 Mar 10;8:19. PMID: 19284555
14. Huang et al. δ-Catenin promotes tumorigenesis and metastasis of lung adenocarcinoma. Oncol Rep. 2018 Feb;39(2):809-817. PMID: 29251319
15. Pan et al. The TET2 interactors and their links to hematological malignancies. IUBMB Life. 2015 Jun;67(6):438-45. PMID: 26099018
16. An et al. TET family dioxygenases and DNA demethylation in stem cells and cancers. Exp. Mol. Med. 2017 Apr 28;49(4):e323. PMID: 28450733
17. Rasmussen et al. Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev. 2016 Apr 1;30(7):733-50. PMID: 27036965
18. Ko et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature. 2010 Dec 9;468(7325):839-43. PMID: 21057493
19. Solary et al. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014 Mar;28(3):485-96. PMID: 24220273
20. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
21. Kosmider et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood. 2009 Oct 8;114(15):3285-91. PMID: 19666869
22. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
23. Lundberg et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014 Apr 3;123(14):2220-8. PMID: 24478400
24. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
25. Peschon et al. Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. J Exp Med. 1994 Nov 1;180(5):1955-60. PMID: 7964471
26. Kim et al. Oncogenic IL7R is downregulated by histone deacetylase inhibitor in esophageal squamous cell carcinoma via modulation of acetylated FOXO1. Int J Oncol. 2018 Jul;53(1):395-403. PMID: 29749437
27. Campos et al. Deleterious and Oncogenic Mutations in the IL7RA. Cancers (Basel). 2019 Dec 5;11(12). PMID: 31817502
28. Harvey et al. Clinical diagnostics and treatment strategies for Philadelphia chromosome-like acute lymphoblastic leukemia. Blood Adv. 2020 Jan 14;4(1):218-228. PMID: 31935290
29. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
30. NCCN Guidelines® - NCCN-Pediatric Acute Lymphoblastic Leukemia [Version 1.2026]

References (continued)

31. Roberts et al. Outcomes of children with BCR-ABL1–like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. J Clin Oncol. 2014 Sep 20;32(27):3012-20. PMID: 25049327
32. Zhang et al. Role of RASA1 in cancer: A review and update (Review). Oncol Rep. 2020 Dec;44(6):2386-2396. PMID: 33125148
33. King et al. Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. Sci Signal. 2013 Feb 26;6(264):re1. PMID: 23443682
34. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev . 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
35. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. J. Clin. Invest. 2012 Feb;122(2):425-34. PMID: 22293180
36. Dyson. RB1: a prototype tumor suppressor and an enigma. Genes Dev. 2016 Jul 1;30(13):1492-502. PMID: 27401552
37. Cobrinik. Pocket proteins and cell cycle control. Oncogene. 2005 Apr 18;24(17):2796-809. PMID: 15838516
38. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam. Cancer. 2012 Jun;11(2):225-33. PMID: 22205104
39. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. . Oman J Ophthalmol . May-Aug 2016;9(2):116-8. PMID: 27433042
40. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. Leukemia. 1999 Sep;13(9):1367-73. PMID: 10482987
41. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. Ophthalmology. 2007 Jul;114(7):1378-83. PMID: 17613328
42. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
43. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
44. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
45. 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
46. 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
47. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
48. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
49. 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
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
52. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
53. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430
54. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
55. Yuan et al. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. Oncogene. 2019 Aug;38(34):6172-6183. PMID: 31285550
56. Colebatch et al. TERT gene: its function and dysregulation in cancer. J Clin Pathol. 2019 Apr;72(4):281-284. PMID: 30696697
57. Mizukoshi et al. Telomerase-Targeted Cancer Immunotherapy. Int J Mol Sci. 2019 Apr 12;20(8). PMID: 31013796
58. NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2025]
59. Arita et al. TERT promoter mutation confers favorable prognosis regardless of 1p/19q status in adult diffuse gliomas with IDH1/2 mutations. Acta Neuropathol Commun. 2020 Nov 23;8(1):201. PMID: 33228806
60. Rauen. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355-69. PMID: 23875798

References (continued)

61. Nelson et al. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood. 2014 May 15;123(20):3152-5. doi: 10.1182/blood-2013-06-511139. Epub 2014 Mar 20. PMID: 24652991
62. 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
63. 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
64. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell. Physiol. Biochem. 2018;51(6):2647-2693. PMID: 30562755
65. Stamos et al. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a007898. PMID: 23169527
66. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. Mol Cancer. 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
67. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J. Cell. Sci. 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
68. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum. Mol. Genet. 1992 Jul;1(4):229-33. PMID: 1338904
69. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
70. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc. Natl. Acad. Sci. U.S.A. 2000 Mar 28;97(7):3352-7. PMID: 10737795
71. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. Nucleic Acids Res. 1998 Jan 1;26(1):269-70. PMID: 9399850
72. 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
73. 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
74. 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
75. 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
76. Pham et al. MAP3K1: Genomic Alterations in Cancer and Function in Promoting Cell Survival or Apoptosis. Genes Cancer. 2013 Nov;4(11-12):419-26. PMID: 24386504
77. Stratikos et al. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer predisposition. Front Oncol. 2014;4:363. PMID: 25566501
78. López. How ERAP1 and ERAP2 Shape the Peptidomes of Disease-Associated MHC-I Proteins. Front Immunol. 2018;9:2463. PMID: 30425713
79. Serwold et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. Nature. 2002 Oct 3;419(6906):480-3. PMID: 12368856
80. Cui et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. J Clin Invest. 2002 Aug;110(4):515-26. PMID: 12189246
81. Cui et al. Shedding of the type II IL-1 decoy receptor requires a multifunctional aminopeptidase, aminopeptidase regulator of TNF receptor type 1 shedding. J Immunol. 2003 Dec 15;171(12):6814-9. PMID: 14662887
82. Mehta et al. Genetic variation of antigen processing machinery components and association with cervical carcinoma. Genes Chromosomes Cancer. 2007 Jun;46(6):577-86. PMID: 17366619
83. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014 Sep;13(9):673-91. PMID: 25131830
84. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. Biomed Pharmacother. 2016 Dec;84:284-290. PMID: 27665474
85. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. Cold Spring Harb Perspect Med. 2016 Oct 3;6(10). PMID: 27599530
86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf

References (continued)

88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
89. https://biodexapharma.com/fast-track-designation-granted-to-mtx110-development-for-the-treatment-of-recurrent-glioblastoma/
90. Hwang et al. Cyclin E in normal and neoplastic cell cycles. Oncogene. 2005 Apr 18;24(17):2776-86. PMID: 15838514
91. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
92. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
93. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
94. Schraml et al. Cyclin E overexpression and amplification in human tumours. J. Pathol. 2003 Jul;200(3):375-82. PMID: 12845634
95. Bai et al. Proliferation profile of classical Hodgkin's lymphomas. Increased expression of the protein cyclin D2 in Hodgkin's and Reed-Sternberg cells. Mod. Pathol. 2004 Nov;17(11):1338-45. PMID: 15354186
96. https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda
97. Keyomarsi et al. Cyclin E and survival in patients with breast cancer. N. Engl. J. Med. 2002 Nov 14;347(20):1566-75. PMID: 12432043
98. Zhao et al. Prognostic Values of CCNE1 Amplification and Overexpression in Cancer Patients: A Systematic Review and Meta-analysis. J Cancer. 2018;9(13):2397-2407. PMID: 30026836
99. Huang et al. Meta-analysis for cyclin E in lung cancer survival. Clin. Chim. Acta. 2012 Apr 11;413(7-8):663-8. PMID: 22244930
100. Sparks et al. Targeting mTOR: prospects for mTOR complex 2 inhibitors in cancer therapy. Oncogene. 2010 Jul 1;29(26):3733-44. PMID: 20418915
101. Saxton et al. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017 Mar 9;168(6):960-976. PMID: 28283069
102. Pópulo et al. The mTOR signalling pathway in human cancer. Int J Mol Sci. 2012;13(2):1886-918. PMID: 22408430
103. Faes et al. Resistance to mTORC1 Inhibitors in Cancer Therapy: From Kinase Mutations to Intratumoral Heterogeneity of Kinase Activity. Oxid Med Cell Longev. 2017;2017:1726078. Epub 2017 Feb 9. PMID: 28280521
104. Mendoza et al. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem. Sci. 2011 Jun;36(6):320-8. PMID: 21531565
105. Hua et al. Targeting mTOR for cancer therapy. J Hematol Oncol. 2019 Jul 5;12(1):71. PMID: 31277692
106. Jebali et al. The role of RICTOR downstream of receptor tyrosine kinase in cancers. Mol Cancer. 2018 Feb 19;17(1):39. PMID: 29455662
107. Bang et al. Correlation between RICTOR overexpression and amplification in advanced solid tumors. PMID: 31740232
108. Kaibori et al. Influence of Rictor and Raptor Expression of mTOR Signaling on Long-Term Outcomes of Patients with Hepatocellular Carcinoma. Dig. Dis. Sci. 2015 Apr;60(4):919-28. PMID: 25371154
109. Wen et al. Rictor is an independent prognostic factor for endometrial carcinoma. Int J Clin Exp Pathol. 2014;7(5):2068-78. PMID: 24966915
110. Deshpande et al. Rad50 ATPase activity is regulated by DNA ends and requires coordination of both active sites. Nucleic Acids Res. 2017 May 19;45(9):5255-5268. PMID: 28369545
111. Kinoshita et al. RAD50, an SMC family member with multiple roles in DNA break repair: how does ATP affect function?. Chromosome Res. 2009;17(2):277-88. PMID: 19308707
112. Rupnik et al. The MRN complex. Curr. Biol. 2008 Jun 3;18(11):R455-7. PMID: 18522810
113. Assenmacher et al. MRE11/RAD50/NBS1: complex activities. Chromosoma. 2004 Oct;113(4):157-66. PMID: 15309560
114. Hopfner et al. The Rad50 zinc-hook is a structure joining Mre11 complexes in DNA recombination and repair. Nature. 2002 Aug 1;418(6897):562-6. PMID: 12152085
115. 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
116. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
117. Fan et al. RAD50 germline mutations are associated with poor survival in BRCA1/2-negative breast cancer patients. Int. J. Cancer. 2018 Oct 15;143(8):1935-1942. PMID: 29726012
118. Brandt et al. Lack of MRE11-RAD50-NBS1 (MRN) complex detection occurs frequently in low-grade epithelial ovarian cancer. BMC Cancer. 2017 Jan 10;17(1):44. PMID: 28073364
119. Wang et al. RAD50 Expression Is Associated with Poor Clinical Outcomes after Radiotherapy for Resected Non-small Cell Lung Cancer. Clin. Cancer Res. 2018 Jan 15;24(2):341-350. PMID: 29030353

References (continued)

120. Zhang et al. Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer. Gynecol. Oncol. 2016 Apr;141(1):57-64. PMID: 27016230
121. Muñoz et al. Coordination of structure-specific nucleases by human SLX4/BTBD12 is required for DNA repair. Mol. Cell. 2009 Jul 10;35(1):116-27. PMID: 19595721
122. Guervilly et al. SLX4: multitasking to maintain genome stability. Crit. Rev. Biochem. Mol. Biol. 2018 Oct;53(5):475-514. PMID: 30284473
123. Andersen et al. Drosophila MUS312 and the vertebrate ortholog BTBD12 interact with DNA structure-specific endonucleases in DNA repair and recombination. Mol. Cell. 2009 Jul 10;35(1):128-35. PMID: 19595722
124. Baird et al. The Molecular Mechanisms Regulating the KEAP1-NRF2 Pathway. Mol Cell Biol. 2020 Jun 15;40(13). PMID: 32284348
125. Suzuki et al. Toward clinical application of the Keap1-Nrf2 pathway. Trends Pharmacol. Sci. 2013 Jun;34(6):340-6. PMID: 23664668
126. Ohta et al. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. Cancer Res. 2008 Mar 1;68(5):1303-9. PMID: 18316592
127. Rojo et al. NRF2 and the Hallmarks of Cancer. Cancer Cell. 2018 Jul 9;34(1):21-43. PMID: 29731393
128. So et al. The TNF-TNFR Family of Co-signal Molecules. Adv Exp Med Biol. 2019;1189:53-84. PMID: 31758531
129. Costello et al. Stimulation of non-Hodgkin's lymphoma via HVEM: an alternate and safe way to increase Fas-induced apoptosis and improve tumor immunogenicity. Leukemia. 2003 Dec;17(12):2500-7. PMID: 14562115
130. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
131. Launay et al. High rate of TNFRSF14 gene alterations related to 1p36 region in de novo follicular lymphoma and impact on prognosis. Leukemia. 2012 Mar;26(3):559-62. PMID: 21941365
132. Cheung et al. Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis. Cancer Res. 2010 Nov 15;70(22):9166-74. PMID: 20884631
133. Lu et al. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. Pharmacol. Rev. 2006 Dec;58(4):782-97. PMID: 17132855
134. Davey et al. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. Clin Biochem Rev. 2016 Feb;37(1):3-15. PMID: 27057074
135. Crumbaker et al. AR Signaling and the PI3K Pathway in Prostate Cancer. Cancers (Basel). 2017 Apr 15;9(4). PMID: 28420128
136. Leung et al. Non-Genomic Actions of the Androgen Receptor in Prostate Cancer. . Front Endocrinol (Lausanne). 2017 Jan 17;8:2. . PMID: 28144231
137. Waltering et al. Androgen receptor (AR) aberrations in castration-resistant prostate cancer. Mol. Cell. Endocrinol. 2012 Sep 5;360(1-2):38-43. PMID: 22245783
138. Antonarakis et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N. Engl. J. Med. 2014 Sep 11;371(11):1028-38. PMID: 25184630
139. Zhu et al. Novel Junction-specific and Quantifiable In Situ Detection of AR-V7 and its Clinical Correlates in Metastatic Castration-resistant Prostate Cancer. Eur. Urol. 2018 May;73(5):727-735. PMID: 28866255
140. https://www.cancernetwork.com/view/fda-grants-fast-track-designation-to-enobosarm-in-ar-er-her2--metastatic-breast-cancer
141. https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA
142. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202379s035lbl.pdf
143. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203415s024,213674s012lbl.pdf
144. NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 5.2025]
145. Lallous et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol. 2016 Jan 26;17:10. PMID: 26813233
146. Robinson et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015 May 21;161(5):1215-1228. PMID: 26000489
147. Cheung et al. Targeting therapeutic liabilities engendered by PIK3R1 mutations for cancer treatment. Pharmacogenomics. 2016 Feb;17(3):297-307. PMID: 26807692
148. Cantley. The phosphoinositide 3-kinase pathway. Science. 2002 May 31;296(5573):1655-7. PMID: 12040186
149. Fruman et al. The PI3K Pathway in Human Disease. Cell. 2017 Aug 10;170(4):605-635. PMID: 28802037

References (continued)

150. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 2006 Aug;7(8):606-19. PMID: 16847462
151. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. Nat. Rev. Mol. Cell Biol. 2012 Feb 23;13(3):195-203. PMID: 22358332
152. Chagpar et al. Direct positive regulation of PTEN by the p85 subunit of phosphatidylinositol 3-kinase. Proc. Natl. Acad. Sci. U.S.A. 2010 Mar 23;107(12):5471-6. PMID: 20212113
153. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
154. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
155. 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
156. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
157. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
158. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
159. 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
160. 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
161. 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
162. 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
163. 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
164. 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
165. 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
166. 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
167. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
168. 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
169. 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
170. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]
171. 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
172. Goldstein et al. Recurrent Loss of NFE2L2 Exon 2 Is a Mechanism for Nrf2 Pathway Activation in Human Cancers. Cell Rep. 2016 Sep 6;16(10):2605-2617. PMID: 27568559
173. https://ir.calithera.com//news-releases/news-release-details/calithera-receives-fda-fast-track-designation-sapanisertib
174. Rodgers et al. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. Biosci Rep. 2017 Feb 28;37(1). PMID: 28082369
175. Wang et al. Inositol Polyphosphate 4-Phosphatase Type II Is a Tumor Suppressor in Multiple Myeloma. Front Oncol. 2021;11:785297. PMID: 35070988
176. Yang et al. INPP4B exerts a dual function in the stemness of colorectal cancer stem-like cells through regulating Sox2 and Nanog expression. Carcinogenesis. 2020 Mar 13;41(1):78-90. PMID: 31179504

References (continued)

177. Woolley et al. Phosphoinositide signaling in cancer: INPP4B Akt(s) out. Trends Mol Med. 2015 Sep;21(9):530-2. PMID: 26150301