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

Patient Name: 김형근
Gender: M
Sample ID: N25-90

Primary Tumor Site: prostate
Collection Date: 2025.06.25

Sample Cancer Type: Prostate Cancer

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Report Highlights

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Relevant Prostate Cancer Findings

Gene	Finding
EGFR	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***5.7 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CDK12 p.(L123Tfs*4) c.366_367insA* cyclin dependent kinase 12 Allele Frequency: 33.38% Locus: chr17:37618689 Transcript: NM_016507.4	None*	bevacizumab + olaparib II+ niraparib II+	11
IIC	*RAD54L p.(R365*) c.1093C>T* RAD54 like (S. cerevisiae) Allele Frequency: 52.54% Locus: chr1:46736381 Transcript: NM_001142548.1	None*	bevacizumab + olaparib II+ niraparib II+	11
IIC	*TP53 p.(R175H) c.524G>A* tumor protein p53 Allele Frequency: 23.35% Locus: chr17:7578406 Transcript: NM_000546.6	None*	None*	3

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
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

*ATRX p.(A1410Qfs*80) c.4224delG, JAK3 p.(R103C) c.307C>T, Microsatellite stable, NF1 deletion, PIK3R1 deletion, RNASEH2B deletion, STAG2 p.(R604*) c.1810C>T, STAT5B p.(R654Q) c.1961G>A, TP53 p.(Y220S) c.659A>C, UGT1A1 p.(G71R) c.211G>A, TET2 deletion, NOTCH4 p.(L15Yfs*27) c.43_46delCTGC, JAK2 deletion, CHD4 p.(R877W) c.2629C>T, ZFHX3 deletion, DDX3X p.(R263H) c.788G>A, ZMYM3 p.(R1267*) c.3799C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CDK12	p.(L123Tfs*4)	c.366_367insA	.	chr17:37618689	33.38%	NM_016507.4	frameshift Insertion
RAD54L	p.(R365*)	c.1093C>T	.	chr1:46736381	52.54%	NM_001142548.1	nonsense
TP53	p.(R175H)	c.524G>A	COSM10648	chr17:7578406	23.35%	NM_000546.6	missense
ATRX	p.(A1410Qfs*80)	c.4224delG	.	chrX:76909680	2.11%	NM_000489.6	frameshift Deletion
JAK3	p.(R103C)	c.307C>T	.	chr19:17954587	2.55%	NM_000215.4	missense
STAG2	p.(R604*)	c.1810C>T	.	chrX:123197044	4.64%	NM_001042749.2	nonsense
STAT5B	p.(R654Q)	c.1961G>A	.	chr17:40359692	4.19%	NM_012448.4	missense
TP53	p.(Y220S)	c.659A>C	COSM43850	chr17:7578190	30.74%	NM_000546.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	53.15%	NM_000463.3	missense
NOTCH4	p.(L15Yfs*27)	c.43_46delCTGC	.	chr6:32191659	99.71%	NM_004557.4	frameshift Deletion
CHD4	p.(R877W)	c.2629C>T	COSM431706	chr12:6702280	2.86%	NM_001273.5	missense
DDX3X	p.(R263H)	c.788G>A	.	chrX:41203305	4.79%	NM_001356.5	missense
ZMYM3	p.(R1267*)	c.3799C>T	.	chrX:70462023	2.72%	NM_201599.3	nonsense
EPHA2	p.(R657Q)	c.1970G>A	.	chr1:16459758	2.73%	NM_004431.5	missense
JAK1	p.(E791K)	c.2371G>A	.	chr1:65309779	2.79%	NM_002227.4	missense
BRINP3	p.(R56H)	c.167G>A	.	chr1:190423854	2.54%	NM_199051.3	missense
ASAP2	p.(A541T)	c.1621G>A	.	chr2:9514948	2.68%	NM_003887.3	missense
REG3G	p.(K45E)	c.133A>G	.	chr2:79253895	2.77%	NM_001008387.3	missense
PDE1A	p.(D55G)	c.164A>G	.	chr2:183129091	2.77%	NM_001258312.1	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PDCD1	p.(R86H)	c.257G>A	.	chr2:242794952	4.55%	NM_005018.3	missense
ATR	p.(V505A)	c.1514T>C	.	chr3:142279132	3.42%	NM_001184.4	missense
ANKRD17	p.(S2204G)	c.6610A>G	.	chr4:73956735	56.51%	NM_032217.5	missense
CTNND2	p.(S1039L)	c.3116C>T	.	chr5:10992758	2.76%	NM_001332.4	missense
JAK2	p.(F512L)	c.1534T>C	.	chr9:5069945	3.72%	NM_004972.4	missense
RASEF	p.(R262Y)	c.784_785delCGinsTA	.	chr9:85627407	1.91%	NM_152573.4	missense
PLXDC2	p.(R154W)	c.460C>T	.	chr10:20335933	2.55%	NM_032812.9	missense
YAP1	p.(R349H)	c.1046G>A	.	chr11:102094366	2.53%	NM_001130145.3	missense
KMT2A	p.(P2128L)	c.6383C>T	.	chr11:118372450	3.78%	NM_001197104.2	missense
KMT2D	p.(L3931F)	c.11791C>T	.	chr12:49426697	17.83%	NM_003482.4	missense
KMT2D	p.(E3046K)	c.9136G>A	.	chr12:49432003	3.99%	NM_003482.4	missense
TMEM132D	p.(D460N)	c.1378G>A	.	chr12:129694130	2.42%	NM_133448.3	missense
POLE	p.(A1854V)	c.5561C>T	.	chr12:133214717	38.97%	NM_006231.4	missense
SYT16	p.(S500L)	c.1499C>T	.	chr14:62550978	2.29%	NM_001367661.1	missense
MAP2K1	p.(S231L)	c.692C>T	.	chr15:66774216	2.61%	NM_002755.4	missense
ZFHX3	p.(L499V)	c.1495T>G	.	chr16:72992550	2.67%	NM_006885.4	missense
ZFHX3	p.(D448N)	c.1342G>A	.	chr16:72992703	3.51%	NM_006885.4	missense
NCOR1	p.(R187H)	c.560G>A	.	chr17:16068351	3.03%	NM_006311.4	missense
NF1	p.(V54I)	c.160G>A	.	chr17:29483100	3.63%	NM_001042492.3	missense
NF1	p.(R385C)	c.1153C>T	.	chr17:29528145	2.96%	NM_001042492.3	missense
RNF43	p.(R296H)	c.887G>A	.	chr17:56437575	3.02%	NM_017763.6	missense
SOX9	p.(L506P)	c.1517T>C	.	chr17:70120515	3.21%	NM_000346.4	missense
KMT2B	p.(P670del)	c.2009_2011delCTC	.	chr19:36212249	56.96%	NM_014727.3	nonframeshift Deletion
KMT2B	p.(R1784W)	c.5350C>T	.	chr19:36221681	2.73%	NM_014727.3	missense
AXL	p.(N266D)	c.796_798delAACinsGAT	.	chr19:41743861	1.85%	NM_021913.5	missense
BCOR	p.(N1267K)	c.3801C>G	.	chrX:39922907	2.85%	NM_001123385.2	missense
BCOR	p.(R1163Q)	c.3488G>A	.	chrX:39923603	10.28%	NM_001123385.2	missense
USP9X	p.(G1028S)	c.3082G>A	.	chrX:41031145	4.82%	NM_001039590.3	missense
RBM10	p.(R960Q)	c.2879G>A	.	chrX:47045889	3.23%	NM_001204468.1	missense
BTK	p.(R490C)	c.1468C>T	.	chrX:100611138	4.60%	NM_000061.3	missense
STAG2	p.(R1186Q)	c.3557G>A	.	chrX:123224793	2.62%	NM_001042749.2	missense

Variant Details (continued)

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
RB1	chr13:48877953	1.03	0.66
NF1	chr17:29422233	1.14	0.7
PIK3R1	chr5:67522468	1.13	0.7
RNASEH2B	chr13:51484145	1.04	0.66
TET2	chr4:106155068	1.01	0.65
JAK2	chr9:5021954	1.03	0.66
ZFHX3	chr16:72820995	1.09	0.68
CD274	chr9:5456050	1.09	0.68
RNASEH2C	chr11:65487230	6.27	2.49

Biomarker Descriptions

CDK12 p.(L123Tfs*4) c.366_367insA, RAD54L p.(R365*) c.1093C>T

RAD54 like (S. cerevisiae), cyclin dependent kinase 12

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA[164]. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs[164,165]. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2[166,167,168,169]. A consequence of HRD due to the failure to repair DSBs is genomic instability[170,171]. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division[172,173,174,175,176,177]. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)[173,178,179]. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability[172]. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible[180,181,182]. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars[183,184]. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)[164,185]. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type[164]. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)[164,170,186,187].

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation[188]. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma[188]. Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[189,190,191,192,193,194,195,196]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[18,19]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma,

Biomarker Descriptions (continued)

renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[18,19].

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies[197,198,199]. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality[164,200,201,202]. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib[203] was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer[203]. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L[167,203,204]. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers[203]. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib[205] (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib[206] (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib[207] (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability[208]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[209], for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex[209] causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported[210]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[211]. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations[211,212,213,214].

TP53 p.(R175H) c.524G>A, TP53 p.(Y220S) c.659A>C

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[100]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[101]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[102,103].

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%)[18,19,104,105,106,107]. 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[18,19]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[108,109,110,111]. Alterations in TP53 are also observed in pediatric cancers[18,19]. 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)[18,19]. 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)[18,19].

Potential relevance: The small molecule p53 reactivator, PC14586[112] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[113], (2019) and breakthrough designation[114] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[115,116]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[39]. 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)[20,23,44,52,53,117]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[118]. 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[119].

Biomarker Descriptions (continued)

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[76,77]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[78]. 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[76,77,79]. 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[80].

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%)[19]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[19]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[81,82,83].

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

ATRX p.(A1410Qfs*80) c.4224delG

ATRX, chromatin remodeler

Background: The ATRX gene encodes the ATRX chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins[1]. The SWI/SNF proteins are a group of DNA translocases that use ATP hydrolysis to remodel chromatin structure and maintain genomic integrity by controlling transcriptional regulation, DNA repair, and chromosome stability through the regulation of telomere length[30,31,32,33]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[34,35,36].

Alterations and prevalence: Somatic mutations of ATRX are observed in 38% of brain lower grade glioma, 15% of uterine corpus endometrial carcinoma, 14% of sarcoma, 9% of glioblastoma multiforme and skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of lung adenocarcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma, 5% of bladder urothelial carcinoma and lung squamous cell carcinoma, 4% of adrenocortical carcinoma, head and neck squamous cell carcinoma and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, pheochromocytoma and paraganglioma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma and kidney chromophobe[18,19]. Biallelic deletion of ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[18,19]. Although alterations of ATRX in pediatric populations are rare, somatic mutations are observed in 6% of gliomas, 4% of bone cancer, 3% of soft tissue sarcoma, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (3 in 332 cases), and leukemia (2 in 354 cases)[19]. Biallelic deletion of ATRX is observed in 1% of peripheral nervous system tumors (1 in 91 cases) in and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[19].

Potential relevance: Currently, no therapies are approved for ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[37,38]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[39,40].

JAK3 p.(R103C) c.307C>T

Janus kinase 3

Background: The JAK3 gene encodes Janus kinase 3, a non-receptor protein tyrosine kinase (PTK)[1,2]. JAK3 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[2]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[3]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[3,4,5].

Alterations and prevalence: Recurrent somatic mutations in JAK3 have been observed in T-cell lymphomas and acute lymphoblastic leukemia (ALL)[25,26]. Mutations in the pseudokinase domain (M511I, A573V, R657W), and kinase domain (L857Q) activate the JAK/STAT pathway and transform hematopoietic cells in vitro[25]. These variants are infrequently observed in solid cancers[18]. Somatic mutations in JAK3 are observed in 8% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma and uterine carcinosarcoma, 3% of adrenocortical carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma, cervical squamous cell carcinoma, liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and esophageal adenocarcinoma[18,19]. JAK3 is amplified in 6% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma

Biomarker Descriptions (continued)

and cholangiocarcinoma, and 2% of mesothelioma and esophageal adenocarcinoma[18,19]. Alterations in JAK3 are rare in pediatric cancers[18,19]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases), and 1% of leukemia (4 in 354 cases), and less than 1% of glioma (2 in 297 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), bone cancer (1 in 327 cases), embryonal tumors (1 in 332 cases), and peripheral nervous system tumors (1 in 1158 cases)[18,19]. Amplification of JAK3 is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[18,19].

Potential relevance: Currently, no therapies are approved for JAK3 aberrations. Tofacitinib (2012), a JAK3 inhibitor, is FDA approved for rheumatoid and psoriatic arthritis[27]. Activating mutations in JAK3, including the germline variant V722I, promoted increased expression of PD-L1 in lung cancer and were associated with durable benefit from tofacitinib PD-L1 blockade[28]. JAK3 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia in adults and children[12,23,29].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[142]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[143,144]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[145]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[146]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[146]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[147,148,149,150,151]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[144]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[143,144,148,152].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[143,144,153,154]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[153,154].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[155] (2014) and nivolumab[156] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[155] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[155]. Dostarlimab[157] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[149,158]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[159] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[149,160,161]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[161]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[162,163]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[162,163].

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[41]. 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[41,42]. 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[41]. 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)[41,43,44].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[41]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of

Biomarker Descriptions (continued)

carcinogenesis[41,45]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[41,44].

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)[46].

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[94]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[94]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[94]. 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[95,96]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[95,96,97,98]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[99]. 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[94].

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[18]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[18].

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

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[55,56]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[55]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[55].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[18,19]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[18,19].

Potential relevance: Currently, no therapies are approved for RNASEH2B aberrations.

STAG2 p.(R604*) c.1810C>T

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[47,48]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[49,50]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[49,51].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[44]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[19]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[19,44].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[44,52,53]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[54].

Biomarker Descriptions (continued)

STAT5B p.(R654Q) c.1961G>A

signal transducer and activator of transcription 5B

Background: The STAT5B gene encodes the signal transducer and activator of transcription 5B. STAT5B, a transcription factor, is a member of a highly conserved signal transducer and activator of transcription (STAT) family which also includes STAT1-4, STAT5A, and STAT6[70]. Inactive STAT transcription factors in the cytoplasm are activated by tyrosine phosphorylation, resulting in STAT dimerization and nuclear translocation[70]. Following translocation to the nucleus, STAT dimers interact with specific enhancers and promote transcriptional initiation of target genes[70]. STAT5B is activated following ligand mediated receptor stimulation by erythropoietin, prolactin, interleukins, and other growth factors[71]. Constitutively activated STAT5B promotes tumor growth and survival, suggesting an oncogenic role for STAT5B[71].

Alterations and prevalence: Mutations in STAT5B are observed in 5% of melanoma, 3% of stomach and uterine cancer, and 2% of colorectal cancer[18,19]. The missense mutation, N642H, is commonly observed in hematological malignancies and specifically promotes aggressive T-cell leukemia/lymphoma[72,73].

Potential relevance: Currently, no therapies are approved for STAT5B aberrations.

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,84]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[84,85]. 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[86]. 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[86,87,88,89]. 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[90].

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[18,19].

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

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[64]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[65,66]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[67]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[64,65,66]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[44]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[65,68]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

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[20]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[20,69]

Biomarker Descriptions (continued)

NOTCH4 p.(L15Yfs*27) c.43_46delCTGC

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[57]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[58,59]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[60,61,62,63].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[18].

Potential relevance: Currently, no therapies are approved for NOTCH4 aberrations.

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,2]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[2]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[3]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[3,4,5]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[6,7].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[8,9]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[10,11]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[12,13]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[14,15,16,17]. JAK2 fusions are infrequently observed in solid tumors[18]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[18]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[18,19]. Alterations in JAK2 are also observed in pediatric cancers[18,19]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[18,19]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[18,19]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[18,19].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[20,21]. Ruxolitinib[22] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[23]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[24]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[14,15,16,17].

CHD4 p.(R877W) c.2629C>T

chromodomain helicase DNA binding protein 4

Background: The CHD4 gene encodes the chromodomain helicase DNA binding protein 4[1]. CHD4 belongs to the CHD subfamily of proteins that function in the maturation and assembly of pre-nucleosomes into mature octameric nucleosomes and facilitates appropriate spacing of each nucleosome[91]. Specifically, CHD4 promotes chromatin remodeling by stimulating the sliding of nucleosomes along DNA and interfering with DNA-histone association[92]. CHD4 is the ATPase component of the NuRD nucleosome remodeling and deacetylase complex, along with HDAC1, HDAC2, RbAp46, RbAp48, MBD3 or MBD2, GATA2a and GATA2b[92]. The NuRD

Biomarker Descriptions (continued)

complex influences several different regulatory processes, including histone deacetylation, demethylation, nucleosome mobilization, and protein recruitment[92]. Aberrations in CHD4, including mutations, have been observed to promote cancer cell stemness in vitro[93].

Alterations and prevalence: Somatic mutations in CHD4 are observed in 22% of uterine corpus endometrial carcinoma, 18% of uterine carcinosarcoma, 9% of skin cutaneous melanoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[18,19]. CHD4 is amplified in 6% of testicular germ cell tumor and ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma and brain lower grade glioma, 3% of pancreatic adenocarcinoma, and 2% of lung squamous cell carcinoma, uterine corpus endometrial carcinoma, bladder urothelial carcinoma, sarcoma, breast invasive carcinoma, esophageal adenocarcinoma, and glioblastoma multiforme[18,19].

Potential relevance: Currently, no therapies are approved for CHD4 aberrations.

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,120,121]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[121,122]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[123,124,125,126,127]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[123,126,128,129].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[18,19]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[18,19].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

DDX3X p.(R263H) c.788G>A

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II[1,130]. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)[130,131,132,133]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[130]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[134,135,136,137,138,139,140,141]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[134].

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma[18,19]. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma[18,19].

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

ZMYM3 p.(R1267*) c.3799C>T

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[74].

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

Biomarker Descriptions (continued)

squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[18,19]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[75]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[18,19].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-04-16. For the most up-to-date information, search www.fda.gov.

CDK12 p.(L123Tfs*4) c.366_367insA

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer **Variant class:** HR Deficient

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

RAD54L p.(R365*) c.1093C>T

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer **Variant class:** HR Deficient

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

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

CDK12 p.(L123Tfs*4) c.366_367insA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	✖	✖	✖	○	● (II)
bevacizumab + olaparib	✖	✖	✖	○	✖
pamiparib	✖	✖	✖	✖	● (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

CDK12 p.(L123Tfs*4) c.366_367insA (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

RAD54L p.(R365*) c.1093C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	✖	✖	✖	○	● (II)
bevacizumab + olaparib	✖	✖	✖	○	✖
pamiparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

TP53 p.(R175H) c.524G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CLSP-1025	✖	✖	✖	✖	● (I)
NT-175, chemotherapy, aldesleukin	✖	✖	✖	✖	● (I)
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

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.

HRR Details

Gene/Genomic Alteration	Finding
CDK12	***INDEL, L123Tfs, AF:0.33***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.05(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 2025-04-16. NCCN information was sourced from www.nccn.org and is current as of 2025-04-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-04-16. ESMO information was sourced from www.esmo.org and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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