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

Patient Name: 오금세
Gender: M
Sample ID: N25-356
Primary Tumor Site: lung
Collection Date: 2024.10.11

Sample Cancer Type: Lung Cancer

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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	***33.71 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*FANCM p.(R486*) c.1456C>T* FA complementation group M Allele Frequency: 3.41% Locus: chr14:45628358 Transcript: NM_020937.4	None*	None*	1
IIC	*RAD50 p.(E1062*) c.3184G>T* RAD50 double strand break repair protein Allele Frequency: 31.94% Locus: chr5:131953781 Transcript: NM_005732.4	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.(M2410) c.7228delA, BCOR p.(W1270*) c.3810G>A, FBXW7 p.(R441W) c.1321C>T, KMT2A p.(R1502*) c.4504C>T, Microsatellite stable, NF1 p.(E2645*) c.7933G>T, STAG2 p.(Q615*) c.1843C>T, TET2 p.(N844Pfs*6) c.2517_2529dup,*

*TP53 p.(L348Ffs*34) c.1043_1044insT, RIT1 amplification, FAT1 p.(R628*) c.1882C>T, RASA1 p.(E166*) c.496G>T, ERAP1 deletion, CSMD3 p.(W1967*) c.5901G>A, TBX3 deletion, NQO1 p.(P187S) c.559C>T, KDM5C p.(E613K) c.1837G>A, TAF1 p.(R1050C) c.3148C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FANCM	p.(R486*)	c.1456C>T	.	chr14:45628358	3.41%	NM_020937.4	nonsense
RAD50	p.(E1062*)	c.3184G>T	.	chr5:131953781	31.94%	NM_005732.4	nonsense
ATRX	p.(M2410*)	c.7228delA	.	chrX:76764079	31.56%	NM_000489.6	nonsense
BCOR	p.(W1270*)	c.3810G>A	.	chrX:39922898	3.57%	NM_001123385.2	nonsense
FBXW7	p.(R441W)	c.1321C>T	COSM34014	chr4:153249457	3.00%	NM_033632.3	missense
KMT2A	p.(R1502*)	c.4504C>T	.	chr11:118360531	3.63%	NM_001197104.2	nonsense
NF1	p.(E2645*)	c.7933G>T	.	chr17:29684350	32.46%	NM_001042492.3	nonsense
STAG2	p.(Q615*)	c.1843C>T	.	chrX:123197719	3.05%	NM_001042749.2	nonsense
TET2	p.(N844Pfs*6)	c.2517_2529dup	.	chr4:106157615	6.40%	NM_001127208.3	frameshift Insertion
TP53	p.(L348Ffs*34)	c.1043_1044insT	.	chr17:7573983	28.09%	NM_000546.6	frameshift Insertion
FAT1	p.(R628*)	c.1882C>T	.	chr4:187629100	4.18%	NM_005245.4	nonsense
RASA1	p.(E166*)	c.496G>T	.	chr5:86564764	16.87%	NM_002890.3	nonsense
CSMD3	p.(W1967*)	c.5901G>A	.	chr8:113402926	3.43%	NM_198123.2	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	34.00%	NM_000903.3	missense
KDM5C	p.(E613K)	c.1837G>A	.	chrX:53231065	6.20%	NM_004187.5	missense
TAF1	p.(R1050C)	c.3148C>T	COSM4171975	chrX:70613247	4.25%	NM_004606.5	missense
DNAJC11	p.([G360=;V361I])	c.1080_1081delTGinsCA	.	chr1:6704634	2.10%	NM_018198.4	synonymous, missense
SPEN	p.(R1137H)	c.3410G>A	.	chr1:16256145	3.16%	NM_015001.3	missense
EPHA2	p.(D495N)	c.1483G>A	.	chr1:16461630	8.57%	NM_004431.5	missense
LRRC7	p.(V647M)	c.1939G>A	.	chr1:70493998	3.30%	NM_001370785.2	missense
ADAM30	p.(D424H)	c.1270G>C	.	chr1:120437690	9.72%	NM_021794.4	missense
OR6F1	p.(I92Yfs*16)	c.273delC	.	chr1:247875784	24.96%	NM_001005286.1	frameshift Deletion
OR2W3	p.(L285P)	c.854T>C	.	chr1:248059742	3.12%	NM_001001957.2	missense
OR2M3	p.(N294K)	c.882C>G	.	chr1:248367251	3.45%	NM_001004689.1	missense
ASXL2	p.(?)	c.776-1G>C	.	chr2:25982515	12.47%	NM_018263.6	unknown
IL37	p.(K124R)	c.371A>G	.	chr2:113675317	3.52%	NM_014439.4	missense
BMPR2	p.(P327L)	c.980C>T	.	chr2:203395529	3.63%	NM_001204.7	missense
ZPLD1	p.(R49T)	c.146G>C	.	chr3:102157429	3.99%	NM_175056.2	missense
FGFR3	p.(P657S)	c.1969C>T	.	chr4:1807993	2.85%	NM_000142.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
DTHD1	p.(S196L)	c.587C>T	.	chr4:36285913	21.43%	NM_001170700.3	missense
FREM3	p.(E1305G)	c.3914A>G	.	chr4:144617915	3.34%	NM_001168235.2	missense
PRDM9	p.(R135I)	c.404G>T	.	chr5:23521184	17.33%	NM_020227.4	missense
HCN1	p.(V613F)	c.1837G>T	.	chr5:45262859	21.33%	NM_021072.4	missense
HCN1	p.(A587S)	c.1759G>T	.	chr5:45267215	12.81%	NM_021072.4	missense
MAP3K1	p.(R405C)	c.1213C>T	.	chr5:56161716	3.70%	NM_005921.2	missense
GCNT4	p.(L438S)	c.1313T>C	.	chr5:74324550	3.26%	NM_001366737.1	missense
APC	p.(G721R)	c.2161G>A	.	chr5:112173452	3.56%	NM_000038.6	missense
APC	p.(S1213L)	c.3638C>T	.	chr5:112174929	3.31%	NM_000038.6	missense
APC	p.(S2417P)	c.7249T>C	.	chr5:112178540	3.74%	NM_000038.6	missense
PCDHGA9	p.(A360T)	c.1078G>A	.	chr5:140783597	3.07%	NM_018921.2	missense
NOTCH4	p.(Q200R)	c.599A>G	.	chr6:32188955	10.48%	NM_004557.4	missense
COQ3	p.(S272A)	c.814_815delAGinsGC	.	chr6:99819378	2.30%	NM_017421.4	missense
PRDM1	p.(G571S)	c.1711G>A	.	chr6:106553746	2.99%	NM_001198.4	missense
FBXO30	p.(L381S)	c.1142T>C	.	chr6:146126400	3.50%	NM_032145.5	missense
ESR1	p.(R243C)	c.727_729delCGTinsTGC	.	chr6:152201873	2.94%	NM_001122740.2	missense
HDAC9	p.(W745C)	c.2235G>T	.	chr7:18832988	6.96%	NM_178425.3	missense
GALNT17	p.(E570*)	c.1708G>T	.	chr7:71177042	19.48%	NM_022479.3	nonsense
ABCB1	p.(V423L)	c.1267G>T	.	chr7:87179570	16.95%	NM_000927.4	missense
SMO	p.(C217*)	c.651_652delCCinsAA	.	chr7:128845157	18.41%	NM_005631.5	nonsense
TAS2R38	p.(A241S)	c.721G>T	.	chr7:141672769	3.61%	NM_176817.5	missense
ADAM18	p.(E311D)	c.933G>T	.	chr8:39502880	14.08%	NM_014237.3	missense
PXDNL	p.(T422N)	c.1265_1266delCAinsAC	.	chr8:52361662	18.02%	NM_144651.5	missense
C8orf89	p.(G64R)	c.190G>A	.	chr8:74169299	3.42%	NM_001243237.1	missense
DCAF4L2	p.(Q277H)	c.831A>C	.	chr8:88885369	40.37%	NM_152418.4	missense
CSMD3	p.(P2687L)	c.8060C>T	.	chr8:113318247	11.00%	NM_198123.2	missense
FAM83A	p.(R234G)	c.700A>G	.	chr8:124206315	3.13%	NM_032899.6	missense
PDCD1LG2	p.(E97K)	c.289G>A	.	chr9:5534978	2.86%	NM_025239.4	missense
MTAP	p.(S232L)	c.695C>T	.	chr9:21859306	2.73%	NM_002451.4	missense
GNAQ	p.(R210M)	c.629G>T	.	chr9:80409485	10.43%	NM_002072.5	missense
FGFR2	p.(E499K)	c.1495G>A	.	chr10:123260406	3.08%	NM_000141.5	missense
FGFR2	p.([V232=;V233A])	c.696_698delAGTinsGGC	.	chr10:123298156	2.47%	NM_000141.5	synonymous, missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
WT1	p.(T310K)	c.929_930delCCinsAA	.	chr11:32439158	16.28%	NM_024426.6	missense
OR5F1	p.(S67F)	c.200C>T	.	chr11:55761902	3.61%	NM_003697.1	missense
OR8I2	p.(A67V)	c.200C>T	.	chr11:55860983	51.80%	NM_001003750.1	missense
OR5R1	p.(K263I)	c.788A>T	.	chr11:56184921	33.16%	NM_001004744.1	missense
CD163	p.(R1075*)	c.3223C>T	.	chr12:7635263	2.93%	NM_004244.5	nonsense
PRIM1	p.(R329C)	c.985C>T	.	chr12:57133145	3.94%	NM_000946.3	missense
FLT3	p.(A896V)	c.2687C>T	.	chr13:28589360	3.39%	NM_004119.3	missense
FLT3	p.(G885V)	c.2654G>T	.	chr13:28589393	14.85%	NM_004119.3	missense
KLF5	p.(R422C)	c.1264C>T	.	chr13:73649914	3.42%	NM_001730.5	missense
FANCM	p.(V193L)	c.577G>C	.	chr14:45606340	2.87%	NM_020937.4	missense
DICER1	p.(D1103E)	c.3309C>G	.	chr14:95570424	9.28%	NM_030621.4	missense
MGA	p.(G2473R)	c.7417G>A	.	chr15:42053955	3.79%	NM_001164273.1	missense
MGA	p.(D2476Y)	c.7426G>T	.	chr15:42053964	4.61%	NM_001164273.1	missense
MGA	p.(C3013R)	c.9037T>C	.	chr15:42059317	3.24%	NM_001164273.1	missense
MAP2K1	p.(R47Q)	c.140G>A	.	chr15:66727424	15.63%	NM_002755.4	missense
CREBBP	p.(V1449I)	c.4345G>A	.	chr16:3788609	3.20%	NM_004380.3	missense
CYLD	p.(A289V)	c.866C>T	.	chr16:50788288	5.51%	NM_001042355.2	missense
ZFHX3	p.([L2726=;E2727K])	c.8178_8179delTGinsCA	.	chr16:72828402	1.96%	NM_006885.4	synonymous, missense
ZFHX3	p.(R2149H)	c.6446G>A	.	chr16:72830135	2.99%	NM_006885.4	missense
NCOR1	p.(P2400S)	c.7198C>T	.	chr17:15935735	4.65%	NM_006311.4	missense
NF1	p.(R1653C)	c.4957C>T	.	chr17:29652959	3.47%	NM_001042492.3	missense
NF1	p.(S2018N)	c.6053G>A	.	chr17:29663397	3.29%	NM_001042492.3	missense
HEATR6	p.(?)	c.2975-1G>T	.	chr17:58121496	52.02%	NM_022070.5	unknown
SMAD4	p.(A327V)	c.980C>T	.	chr18:48591817	4.00%	NM_005359.6	missense
KEAP1	p.(E219D)	c.657G>T	.	chr19:10602921	14.98%	NM_203500.2	missense
NOTCH3	p.(A1613V)	c.4838C>T	.	chr19:15281535	2.88%	NM_000435.3	missense
NOTCH3	p.(D1603N)	c.4807G>A	.	chr19:15281566	2.70%	NM_000435.3	missense
CIC	p.(P1303L)	c.3908C>T	.	chr19:42797856	16.32%	NM_015125.5	missense
RUNX1	p.(Q390R)	c.1169A>G	.	chr21:36164706	4.15%	NM_001754.5	missense
USP9X	p.(P709Q)	c.2126C>A	.	chrX:41025265	5.92%	NM_001039590.3	missense
USP9X	p.(D2338H)	c.7012G>C	.	chrX:41084341	3.82%	NM_001039590.3	missense
USP9X	p.(?)	c.7219-3C>T	.	chrX:41088817	4.47%	NM_001039590.3	unknown
DDX3X	p.(R622H)	c.1865G>A	.	chrX:41206660	4.21%	NM_001356.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
SLC9A7	p.(T624M)	c.1871C>T	.	chrX:46472782	5.26%	NM_001257291.2	missense
KDM5C	p.(M577I)	c.1731G>A	.	chrX:53239611	5.59%	NM_004187.5	missense
KDM5C	p.(K377N)	c.1131G>C	.	chrX:53241080	3.65%	NM_004187.5	missense
AMER1	p.(S941R)	c.2823C>G	.	chrX:63410344	3.67%	NM_152424.4	missense
ATRX	p.(Q606H)	c.1818G>T	.	chrX:76938930	39.24%	NM_000489.6	missense
TGIF2LX	p.(D213N)	c.637G>A	.	chrX:89177721	3.86%	NM_138960.4	missense
NUP62CL	p.(?)	c.530_530+1delinsCA	.	chrX:106396401	2.89%	NM_017681.3	unknown
RTL4	p.(A46T)	c.136G>A	.	chrX:111698092	2.74%	NM_001004308.2	missense
SPANXN3	p.(L91S)	c.272T>C	.	chrX:142596798	2.86%	NM_001009609.4	missense
MPP1	p.(V96A)	c.287T>C	.	chrX:154020082	3.18%	NM_002436.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
RIT1	chr1:155870154	5.78	1.95
ERAP1	chr5:96112128	0.4	0.6
TBX3	chr12:115109599	0.76	0.69

Biomarker Descriptions

FANCM p.(R486*) c.1456C>T

FA complementation group M

Background: The FANCM gene encodes the FA complementation group M protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[27,28]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[27]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[29,30]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[31,32]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[33,34].

Alterations and prevalence: Somatic mutations in FANCM are observed in 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% colorectal adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for FANCM aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCM are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[35].

Biomarker Descriptions (continued)

RAD50 p.(E1062*) c.3184G>T

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[103,104]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[104,105]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[105,106]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[105,106]. 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[105,107]. 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[31,108]. 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[109].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[5,6]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[110].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[111]. 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[111]. 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[112].

ATRX p.(M2410*) c.7228delA

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[39,40,41,42]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[43,44,45].

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[5,6]. Biallelic deletion of ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[5,6]. 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)[6]. 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)[6].

Potential relevance: Currently, no therapies are approved for ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[46,47]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[48,49].

BCOR p.(W1270*) c.3810G>A

BCL6 corepressor

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) co-repressor protein, which potentiates transcriptional repression by BCL6[7,8]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism for BCOR-mediated transcriptional repression independent of BCL6[8]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[9,10,11].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[5,12,13,14]. Higher mutational frequencies are reported in some solid tumors, including

Biomarker Descriptions (continued)

up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma[5,6]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[15,16,17]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[18,19]. Alterations in BCOR are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 13% of soft tissue sarcoma, 4% of glioma, 3% of retinoblastoma, 2% of bone cancer, 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), and Wilms tumor (2 in 710 cases)[5,6]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[15].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR::CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[20,21]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[20]. Somatic mutation in BCOR is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR) and is associated with poor prognosis in AML and MDS[12,13,22,23,24]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse-free survival (RFS) compared to those without BCOR abnormalities (OS = 13.6% vs. 55%; RFS = 14.3% vs. 44.5%)[14]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[25,26].

FBXW7 p.(R441W) c.1321C>T

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[1,136]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes[137]. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[136,137,138,139,140,141,142].

Alterations and prevalence: Somatic mutations in FBXW7 occur at high frequencies in various malignancies, including 39% of uterine carcinosarcoma, 19% of uterine corpus endometrial carcinoma, 17% of colorectal adenocarcinoma, 12% of cervical squamous cell carcinoma, 8% of stomach adenocarcinoma and bladder urothelial carcinoma, 6% of head and neck squamous cell carcinoma and esophageal adenocarcinoma, 4% of lung squamous cell carcinoma and skin cutaneous melanoma, 3% of pancreatic adenocarcinoma, and 2% of lung adenocarcinoma and breast invasive carcinoma[5,6,143,144,145]. Biallelic deletion is observed in 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and brain lower grade glioma[5,6]. Alterations in FBXW7 are also observed in pediatric cancers[6]. Somatic mutations in FBXW7 are observed in 15% of T-lymphoblastic leukemia/lymphoma (6 in 41 cases), 2% of embryonal tumor (5 in 332 cases), and less than 1% of glioma (2 in 297 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and bone cancer (1 in 327 cases)[6]. Biallelic deletion of FBXW7 is observed in 2% of B-lymphoblastic leukemia/lymphoma (12 in 731 cases) and less than 1% of leukemia (2 in 250 cases)[6].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[146], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[143]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus[147].

KMT2A p.(R1502*) c.4504C>T

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1,82]. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily[82]. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis[83]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[84]. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[84]. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[84,85,86,87].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[5,6,84,88]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[84]. KMT2A alterations observed in solid

Biomarker Descriptions (continued)

tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity[5,89]. KMT2A alterations are also observed in pediatric cancers[5,6]. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma[5,6,84,90,91].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[22,23]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[92,93,94]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[73]. KMT2A fusion is also associated with poor risk in adult and pediatric ALL[95,96,97]. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement[98]. In 2024, the FDA approved the oral menin inhibitor, revumenib[99], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[100].

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[148]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[149,150]. 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[151]. 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[152]. 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)[152]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[153,154,155,156,157]. 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[150]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[149,150,154,158].

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[149,150,159,160]. 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[159,160].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[161] (2014) and nivolumab[162] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[161] 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[161]. Dostarlimab[163] (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[155,164]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[165] (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[155,166,167]. 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[167]. 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[168,169]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[168,169].

NF1 p.(E2645*) c.7933G>T

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[50]. 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[50,51]. 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[50]. 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)[12,50,52].

Biomarker Descriptions (continued)

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[50]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[50,53]. Somatic mutations in NF1 are observed in several cancer types including 17% of skin cutaneous melanoma, 14% of uterine corpus endometrial carcinoma, and 12% of glioblastoma multiforme, lung adenocarcinoma, and lung squamous cell carcinoma[5,6]. Structural variants in NF1 are observed in 3% of cholangiocarcioma[5,6]. Biallelic deletion of NF1 is observed in 6% of ovarian serous cystadenocarcinoma, 4% of sarcoma, and 2% of uterine corpus endometrial carcinoma, pheochromocytoma and paraganglioma, lung squamous cell carcinoma, adrenocortical carcinoma, glioblastoma multiforme, uterine carcinosarcoma, and acute myeloid leukemia[5,6]. Alterations in NF1 are also observed in pediatric cancers[6]. Somatic mutations in NF1 are observed in 8% of soft tissue sarcoma (3 in 38 cases), 4% of B-lymphoblastic leukemia/lymphoma (9 in 252 cases), 3% of Hodgkin lymphoma (2 in 61 cases), 2% of glioma (6 in 297 cases), 1% of bone cancer (4 in 327 cases) and leukemia (4 in 354 cases), and less than 1% of peripheral nervous system tumors (7 in 1158 cases), embryonal tumors (2 in 332 cases), and Wilms tumor (1 in 710 cases)[6]. Biallelic deletion of NF1 is observed in 2% of bone cancer (1 in 42 cases) and less than 1% of leukemia (2 in 250 cases), Wilms tumor (1 in 136 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[6].

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)[20].

STAG2 p.(Q615*) c.1843C>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[54,55]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[56,57]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[56,58].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants[12]. Somatic mutations in STAG2 are observed in 14% of bladder cancer, 10% of uterine cancer, 5% of glioblastoma multiforme, 4% of lung adenocarcinoma and skin cutaneous melanoma, 3% of acute myeloid leukemia, stomach adenocarcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma, and 2% of cholangiocarcinoma, diffuse large B-cell lymphoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, uterine carcinosarcoma, breast invasive carcinoma, and esophageal adenocarcinoma[6]. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia[6]. Alterations in STAG2 are also observed in pediatric cancers[6]. Somatic mutations in STAG2 are observed in 10% of bone cancer (34 in 327 cases), 5% of soft tissue sarcoma (2 in 38 cases), 2% of embryonal tumors (5 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases) and peripheral nervous system cancers (1 in 1158 cases)[6]. Structural variants in STAG2 are observed in 2% of leukemia (1 in 64 cases) and less than 1% of bone cancer (1 in 150 cases)[6]. Biallelic deletion of STAG2 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of leukemia (1 in 250 cases)[6].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and acute myeloid leukemia[12,23]. 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[59].

TET2 p.(N844Pfs*6) c.2517_2529dup

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[1,67]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[68,69]. 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)[68,69]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[68,69]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[67,70,71].

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)[12]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[70,72]. 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[5,6]. Alterations in TET2 are also observed in the pediatric population[6]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than

Biomarker Descriptions (continued)

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)[6]. 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)[6].

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[73]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[74]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[75].

TP53 p.(L348Ffs*34) c.1043_1044insT

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[118]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[119]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[120,121].

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%)[5,6,122,123,124,125]. 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[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[126,127,128,129]. Alterations in TP53 are also observed in pediatric cancers[5,6]. 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)[5,6]. 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)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[130] (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[131,132]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[48]. 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)[12,23,73,95,133]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[134]. 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[135].

RIT1 amplification

Ras like without CAAX 1

Background: The RIT1 gene encodes the ras-like without CAAX1 protein[1]. RIT1 is a member of the Ras family, possessing intrinsic GTP hydrolysis activity[113]. Specifically, RIT1 is ubiquitously expressed and plays a role in neuron survival following oxidative stress and dendritic cell retraction[113,114,115]. RIT1 mutations have been shown to activate PI3K and MEK signaling pathways and likely promotes tumorigenesis[116]. Hereditary mutations in RIT1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a type of RASopathy[116,117].

Alterations and prevalence: Somatic mutations in RIT1 are observed in 3% of cholangiocarcinoma, 2% of uterine corpus endometrial carcinoma and lung adenocarcinoma, and 1% of cervical squamous cell carcinoma, skin cutaneous melanoma, and acute myeloid leukemia (AML)[5,6]. Amplifications in RIT1 are observed in 14% of uterine carcinosarcoma, 11% of liver hepatocellular and cholangiocarcinoma, 8% of lung adenocarcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, and 6% of ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for RIT1 aberrations.

Biomarker Descriptions (continued)

FAT1 p.(R628*) c.1882C>T

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,66]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[66]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[66]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[66]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[66].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[5,6]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[5,6]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

RASA1 p.(E166*) c.496G>T

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[101,102]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[101]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[101]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[101]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[101].

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[5,6]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[5,6].

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[76,77]. 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[76,78]. 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[76,79,80]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[76,81].

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[5,6]. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma[5,6].

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

CSMD3 p.(W1967*) c.5901G>A

CUB and Sushi multiple domains 3

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,2]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the

Biomarker Descriptions (continued)

transmembrane and extracellular proteins[2,3]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[2,3]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[2,4].

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[5,6]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

TBX3 deletion

T-box 3

Background: TBX3 encodes T-box transcription factor 3 and belongs to the T-box family of transcription factors which also include TBX1 and TBX2[1,60,61]. T-box family of transcription factors are involved in developmental processes such as embryogenesis and organogenesis[1,60,61,62]. Deregulation of TBX3 has been observed in several cancer types, including breast cancer, cervical cancer, colorectal cancer, gastric cancer, melanoma, ovarian cancer, pancreatic cancer, and prostate cancer, and has been suggested to promote tumorigenesis and invasiveness through involvement in several oncogenic pathways[62,63,64,65].

Alterations and prevalence: Somatic mutations in TBX3 are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, 3% of breast invasive carcinoma, cholangiocarcinoma, and skin cutaneous melanoma, and 2% of lung adenocarcinoma, diffuse large B-cell lymphoma, bladder urothelial carcinoma, lung squamous cell carcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma[5,6]. Amplification of TBX3 is found in 2% of adrenocortical carcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of TBX3 is observed in 1% of prostate adenocarcinoma and brain lower grade glioma[5,6].

Potential relevance: Currently, no therapies are approved for TBX3 aberrations.

KDM5C p.(E613K) c.1837G>A

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,36]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[37]. KDM5C removes methylation of di- and trimethylated histone H3 lysine 4 (H3K4) and is involved in the repression of transcription in response to DNA damage[36,37]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[38].

Alterations and prevalence: Somatic mutations in KDM5C are observed in 9% of uterine corpus endometrial carcinoma, 5% of kidney renal clear cell carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, 4% of lung adenocarcinoma and uterine carcinosarcoma[5,6]. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM5C aberrations.

TAF1 p.(R1050C) c.3148C>T

TATA-box binding protein associated factor 1

Background: TAF1 encodes TATA-box binding protein associated factor 1, which plays a key role transcription initiation[1,170]. TAF1 is the largest subunit of the TFIID complex and serves as a bridge to bring additional TBP-associated factors (TAFs) to promoter regions[170,171]. Biochemically, TAF1 has been shown to have protein kinase activity, ubiquitin-activating and -conjugating activity (E1/E2), and histone acetyltransferase activity[172]. TAF1 is also involved in other cellular processes such as cell cycle regulation and

Biomarker Descriptions (continued)

apoptosis[173,174]. Dysregulation of TAF1 has been observed in several cancer types with overexpression being linked to progression and castration resistance in prostate cancer[170,172,175].

Alterations and prevalence: Somatic mutations in TAF1 are observed in 20% of uterine corpus endometrial carcinoma, 10% of skin cutaneous melanoma, 6% of cervical squamous cell carcinoma, 5% of lung squamous cell carcinoma, 4% of lung adenocarcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma, 3% of adrenocortical carcinoma and bladder urothelial carcinoma, and 2% of head and neck squamous cell carcinoma, breast invasive carcinoma, liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, glioblastoma multiforme, pancreatic adenocarcinoma, and kidney chromophobe[5,6]. Amplification of TAF1 is observed in 2% of sarcoma and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for TAF1 aberrations.

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed (continued)

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

FANCM p.(R486*) c.1456C>T

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

RAD50 p.(E1062*) c.3184G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (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
Not Detected	***Not Applicable***

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

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

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