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

Patient Name: 이지연
Gender: Female
Sample ID: N26-22

Primary Tumor Site: Breast
Collection Date: 2017.06.21.

Sample Cancer Type: Breast Cancer

Report Highlights

7 Relevant Biomarkers
3 Therapies Available
11 Clinical Trials

Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***2.85 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	3
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	3
IIC	*ATM p.(R248*) c.742C>T* ATM serine/threonine kinase Allele Frequency: 2.66% Locus: chr11:108115594 Transcript: NM_000051.4	None*	None*	2
IIC	*BARD1 deletion* BRCA1 associated RING domain 1 Locus: chr2:215593375	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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CHEK1 deletion* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	*FGF19 amplification* fibroblast growth factor 19 Locus: chr11:69513948	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

ERCC4 p.(R692) c.2074C>T, FANCA c.1084-1G>A, FBXW7 p.(R441Q) c.1322G>A, FGF3 amplification, FGF4 amplification, MTOR p.(R2217Q) c.6650G>A, Microsatellite stable, PBRM1 p.(R1160*) c.3478C>T, RAD51B deletion, RICTOR p.(E643K) c.1927G>A, HLA-A deletion, CSMD3 p.(R2442*) c.7324C>T, LARP4B p.(R716Q) c.2147G>A, MGA p.(R1155*) c.3463C>T, GPS2 deletion, SRC amplification, PLCG1 amplification, AMER1 p.(R531*) c.1591C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ATM	p.(R248*)	c.742C>T	.	chr11:108115594	2.66%	NM_000051.4	nonsense
ERCC4	p.(R692*)	c.2074C>T	.	chr16:14041527	2.61%	NM_005236.3	nonsense
FANCA	p.(?)	c.1084-1G>A	.	chr16:89858477	4.48%	NM_000135.4	unknown
FBXW7	p.(R441Q)	c.1322G>A	COSM1052091	chr4:153249456	3.96%	NM_033632.3	missense
MTOR	p.(R2217Q)	c.6650G>A	.	chr1:11184567	2.85%	NM_004958.4	missense
PBRM1	p.(R1160*)	c.3478C>T	.	chr3:52610695	2.74%	NM_018313.5	nonsense
RICTOR	p.(E643K)	c.1927G>A	COSM1437485	chr5:38960005	57.55%	NM_152756.5	missense
CSMD3	p.(R2442*)	c.7324C>T	.	chr8:113331102	3.45%	NM_198123.2	nonsense
LARP4B	p.(R716Q)	c.2147G>A	COSM3665919	chr10:858936	3.58%	NM_015155.3	missense
MGA	p.(R1155*)	c.3463C>T	.	chr15:42019410	2.27%	NM_001164273.1	nonsense
AMER1	p.(R531*)	c.1591C>T	COSM1468851	chrX:63411576	3.20%	NM_152424.4	nonsense
TNFRSF14	p.(R22K)	c.65G>A	.	chr1:2488168	3.33%	NM_003820.3	missense
SPEN	p.(R702Q)	c.2105G>A	.	chr1:16254840	2.81%	NM_015001.3	missense
NOTCH2	p.(R1824C)	c.5470C>T	.	chr1:120462861	2.74%	NM_024408.4	missense
MYCN	p.(G100E)	c.299G>A	.	chr2:16082485	4.07%	NM_005378.6	missense
DNMT3A	p.(E205K)	c.613G>A	.	chr2:25497836	2.83%	NM_022552.5	missense
MSH2	p.(P591S)	c.1771C>T	.	chr2:47702175	3.35%	NM_000251.3	missense
MSH6	p.(G75R)	c.223G>A	.	chr2:48010595	3.70%	NM_000179.3	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
REV1	p.(R122Q)	c.365G>A	.	chr2:100058917	2.56%	NM_016316.4	missense
SF3B1	p.(R337Q)	c.1010G>A	.	chr2:198273200	2.30%	NM_012433.4	missense
CUL3	p.(R642Q)	c.1925G>A	.	chr2:225346713	2.53%	NM_003590.5	missense
CUL3	p.(R305C)	c.913C>T	.	chr2:225371691	3.47%	NM_003590.5	missense
FANCD2	p.(?)	c.492-2A>T	.	chr3:10080961	55.07%	NM_033084.6	unknown
SETD2	p.(E1907K)	c.5719G>A	.	chr3:47125551	3.39%	NM_014159.7	missense
NFKBIZ	p.(R662W)	c.1984C>T	.	chr3:101576184	2.15%	NM_031419.4	missense
FGFR3	p.(R603Q)	c.1808G>A	.	chr4:1807639	2.56%	NM_000142.5	missense
ADAMTS12	p.(G469E)	c.1406G>A	.	chr5:33649000	2.83%	NM_030955.4	missense
PIK3R1	p.(R514C)	c.1540C>T	.	chr5:67590478	2.30%	NM_181523.3	missense
CD83	p.(L68F)	c.202C>T	.	chr6:14131799	3.36%	NM_004233.4	missense
RIPOR2	p.(R859*)	c.2575C>T	.	chr6:24828518	2.85%	NM_014722.5	nonsense
PIM1	p.(?)	c.607+3G>A	.	chr6:37139270	2.74%	NM_002648.4	unknown
PIM1	p.(P210S)	c.628C>T	.	chr6:37140792	2.67%	NM_002648.4	missense
CUL9	p.(D197N)	c.589G>A	.	chr6:43152637	4.10%	NM_015089.4	missense
FYN	p.(R507H)	c.1520G>A	.	chr6:111983027	2.99%	NM_153047.4	missense
LATS1	p.([A549V;P550S])	c.1646_1648delCTCinsTTT	.	chr6:150004577	3.15%	NM_004690.4	missense, missense
ARID1B	p.(P1507L)	c.4520C>T	.	chr6:157521999	4.44%	NM_001371656.1	missense
RSPH3	p.(M297T)	c.890_891delTGinsCA	.	chr6:159399347	1.64%	NM_031924.8	missense
PDE10A	p.(A298V)	c.893C>T	.	chr6:165832228	2.54%	NM_001130690.3	missense
GLI3	p.(V1379I)	c.4135G>A	.	chr7:42004536	3.97%	NM_000168.6	missense
KCND2	p.(S574F)	c.1721C>T	.	chr7:120387740	4.31%	NM_012281.3	missense
ZNF862	p.(E1060K)	c.3178G>A	.	chr7:149559427	3.05%	NM_001099220.3	missense
KMT2C	p.(R4789Q)	c.14366G>A	.	chr7:151836854	2.37%	NM_170606.3	missense
KMT2C	p.(P3900S)	c.11698C>T	.	chr7:151853404	3.09%	NM_170606.3	missense
KMT2C	p.(P860S)	c.2578C>T	.	chr7:151935866	31.25%	NM_170606.3	missense
KMT2C	p.(E765K)	c.2293G>A	.	chr7:151945226	3.23%	NM_170606.3	missense
KMT2C	p.(P420S)	c.1258C>T	.	chr7:151960142	2.85%	NM_170606.3	missense
IKBKB	p.(E157K)	c.469G>A	.	chr8:42162785	3.33%	NM_001556.3	missense
MYC	p.(D227N)	c.679G>A	.	chr8:128751142	2.65%	NM_002467.6	missense
FANCC	p.(R292W)	c.874C>T	.	chr9:97888833	5.04%	NM_000136.3	missense
NOTCH1	p.(D331N)	c.991G>A	.	chr9:139413151	2.30%	NM_017617.5	missense
NOTCH1	p.(C227Y)	c.680G>A	.	chr9:139417364	3.64%	NM_017617.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
DNMBP	p.(R1260*)	c.3778C>T	.	chr10:101645464	3.23%	NM_015221.4	nonsense
KMT2A	p.(P655L)	c.1964C>T	.	chr11:118343838	3.76%	NM_001197104.2	missense
KMT2A	p.(R886Q)	c.2657G>A	.	chr11:118344531	3.02%	NM_001197104.2	missense
KMT2A	p.(P2122S)	c.6364C>T	.	chr11:118372431	3.28%	NM_001197104.2	missense
KMT2A	p.(M2477I)	c.7431G>A	.	chr11:118374038	3.12%	NM_001197104.2	missense
KMT2A	p.(P3011S)	c.9031C>T	.	chr11:118375638	2.62%	NM_001197104.2	missense
CHEK1	p.(L360F)	c.1078C>T	.	chr11:125514140	3.38%	NM_001274.5	missense
ARID2	p.(R310C)	c.928C>T	.	chr12:46230679	2.49%	NM_152641.4	missense
KMT2D	p.(E5484K)	c.16450G>A	.	chr12:49415897	2.55%	NM_003482.4	missense
ANO4	p.(D124N)	c.370G>A	.	chr12:101365102	2.98%	NM_178826.4	missense
ANO4	p.(G650E)	c.1949G>A	.	chr12:101493403	3.03%	NM_178826.4	missense
FANCM	p.(L1149F)	c.3445C>T	.	chr14:45645402	3.32%	NM_020937.4	missense
FANCM	p.(R1204C)	c.3610C>T	.	chr14:45645567	2.23%	NM_020937.4	missense
ZFYVE21	p.(L101Rfs*18)	c.302_303delTCinsG	.	chr14:104194195	1.20%	NM_001198953.1	frameshift Block Substitution
RPAP1	p.(E506K)	c.1516_1518delGAGinsAAA	.	chr15:41819714	2.22%	NM_015540.4	missense
SLC30A4	p.([D305=;P306S])	c.915_916delCCinsTT	.	chr15:45779809	2.65%	NM_013309.6	synonymous, missense
CD276	p.(Q228*)	c.682C>T	.	chr15:73995376	3.86%	NM_001024736.2	nonsense
ERCC4	p.(R490Q)	c.1469G>A	.	chr16:14029258	3.80%	NM_005236.3	missense
CTCF	p.(E348K)	c.1042G>A	.	chr16:67650737	2.30%	NM_006565.4	missense
ZNF276	p.(W277*)	c.830G>A	.	chr16:89789941	3.07%	NM_001113525.2	nonsense
NCOR1	p.(T1672I)	c.5015C>T	.	chr17:15968270	3.25%	NM_006311.4	missense
ZNF557	p.(S389L)	c.1166_1167delCAinsTG	.	chr19:7083628	1.78%	NM_001044387.2	missense
KMT2B	p.(A684V)	c.2051C>T	.	chr19:36212300	7.65%	NM_014727.3	missense
KMT2B	p.(R2491H)	c.7472G>A	.	chr19:36228086	2.99%	NM_014727.3	missense
ARHGAP35	p.(E204K)	c.610G>A	.	chr19:47422542	3.07%	NM_004491.5	missense
GATA5	p.(V276M)	c.826G>A	.	chr20:61040977	2.83%	NM_080473.5	missense
EIF1AX	p.(R46Q)	c.137G>A	.	chrX:20153923	2.98%	NM_001412.4	missense
BCOR	p.(E994K)	c.2980G>A	.	chrX:39931619	3.59%	NM_001123385.2	missense
SMC1A	p.(R923H)	c.2768G>A	.	chrX:53423241	3.00%	NM_006306.4	missense
NAP1L2	p.(D174N)	c.520G>A	.	chrX:72433809	3.03%	NM_021963.4	missense
ATRX	p.(R2197H)	c.6590G>A	.	chrX:76813031	2.60%	NM_000489.6	missense

Variant Details (continued)

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.82
ATM	chr11:108098341	1	0.84
CCND1	chr11:69455949	16.52	3.9
BARD1	chr2:215593375	1	0.82
CHEK1	chr11:125496639	1	0.83
FGF19	chr11:69513948	17.68	4.14
FGF3	chr11:69625020	16.33	3.86
FGF4	chr11:69588019	14.68	3.53
RAD51B	chr14:68290164	1	0.81
HLA-A	chr6:29910229	0	0.57
GPS2	chr17:7216071	0.33	0.66
SRC	chr20:36012492	6	1.8
PLCG1	chr20:39766236	6.4	1.88
ASXL1	chr20:30954155	6.5	1.9
TOP1	chr20:39690023	5.78	1.75
PTPRT	chr20:40710527	6.58	1.92

Biomarker Descriptions

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[9,10]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[9,10]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[11,12,13]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[11,14].

Alterations and prevalence: 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[15,16,17,18,19,20,21,22]. 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, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[5,6].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[23]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[24,25]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[26] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary

Biomarker Descriptions (continued)

peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[26] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[27] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[28] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[28] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib[29] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[30] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib[31] received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[32]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[33]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[34], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

ATM deletion, ATM p.(R248*) c.742C>T

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[88]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[89]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[89,90]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[91]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[39,92]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[93].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[26] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[28] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[92,94,95]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[96]. However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM[97,98]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[34], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[177,178,179]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[177,178]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[177,178,180]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[179,181].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287

Biomarker Descriptions (continued)

and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[5,6,182,183]. These mutations block phosphorylation-dependent nuclear export and proteolysis[184,185,186,187]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[5,6,188]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[189,190]. Alterations in CCND1 are also observed in pediatric cancers[6]. Amplification of CCND1 is observed in 1-3% of peripheral nervous system tumors (3 in 91 cases) and bone cancer (1 in 42 cases) and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[191].

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene[1,124]. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage[1,124,125,126]. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction[1,125,127,128]. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[128,129]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[127]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[130]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[130,131].

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma[5,6]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[26] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[34], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2[1]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[73]. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)[74,75]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[74]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[74,76].

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases[5,77]. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases[5,77].

Potential relevance: The PARP inhibitor, olaparib[26] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[34], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members[99,100]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[99,100]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival[101,102,103]. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation[132,133]. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[132,134].

Alterations and prevalence: FGF19 amplification is observed in 35% of esophageal adenocarcinoma, 23% of head and neck squamous cell carcinoma, 15% of breast invasive carcinoma, 13% of lung squamous cell carcinoma, 11% of cholangiocarcinoma and bladder urothelial carcinoma, 7% of stomach adenocarcinoma and liver hepatocellular carcinoma, 5% of skin cutaneous melanoma and ovarian serous cystadenocarcinoma, 3% of lung adenocarcinoma and cervical squamous cell carcinoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, and prostate adenocarcinoma[5,6]. FGF19 aberrations are also observed in pediatric cancers[6]. FGF19 amplification is observed in 3% of peripheral nervous system cancers (3 in 91 cases), 2% of bone cancer (1 in 42 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6]. Somatic mutations in FGF19 are observed in less than 1% of bone cancer (2 in 327 cases)[6].

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma[135].

ERCC4 p.(R692*) c.2074C>T

ERCC excision repair 4, endonuclease catalytic subunit

Background: The ERCC4 gene encodes ERCC excision repair 4, endonuclease catalytic subunit, also known as XPF[1]. The ERCC4-ERCC1 heterodimer is a structure-specific endonuclease which creates the 5' incision at sites of DNA damage during nucleotide excision repair (NER), while ERCC5 creates the 3' incision[117]. Together with ERCC5, the ERCC4-ERCC1 heterodimer is involved in the removal of damaged DNA, leading to ATR activation and DNA damage repair[117]. Germline mutations in ERCC4 are associated with Xeroderma Pigmentosum (XP) complementation group F, a multisystem degenerative disorder that results in photo-sensitivity and a predisposition to skin cancer[118].

Alterations and prevalence: Somatic mutations in ERCC4 are observed in 8% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, 2% of colorectal adenocarcinoma, lung adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ERCC4 aberrations.

FANCA c.1084-1G>A

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, 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[35,36]. 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[35]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[37,38]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[39,40]. 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[41,42]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[36,42,43,44,45].

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[5]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[5].

Biomarker Descriptions (continued)

Potential relevance: The PARP inhibitor, talazoparib[28] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[46,47]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[45].

FBXW7 p.(R441Q) c.1322G>A

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[1,138]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes[139]. 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[138,139,140,141,142,143,144].

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[5,6,145,146,147]. 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[148], 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[145]. 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[149].

FGF3 amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members[99,100]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[99,100]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival[101,102,103]. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2[104,105]. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers[106,107]. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3[105].

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers[5]. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma[106,107].

Potential relevance: Currently, no therapies are approved for FGF3 aberrations.

FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members[1,100]. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[99,100]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways, thereby influencing cell proliferation, migration, and survival[101,102,103].

Biomarker Descriptions (continued)

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma[5,6]. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer[136,137].

Potential relevance: Currently, no therapies are approved for FGF4 aberrations.

MTOR p.(R2217Q) c.6650G>A

mechanistic target of rapamycin

Background: The MTOR gene encodes the mechanistic target of rapamycin kinase (also known as, mammalian target of rapamycin), which is a member of the phosphatidylinositol 3-kinase (PI3K)-related kinases family of serine/threonine protein kinases[1]. MTOR encodes the catalytic subunit of mTOR Complex 1 (mTORC1) and 2 (mTORC2)[54]. These complexes regulate cell growth by modulating protein synthesis, autophagy, and other metabolic pathways[54]. The mTORC1 and mTORC2 complexes are downstream effectors of the PI3K/AKT/MTOR signaling pathway and facilitate integration of the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK signaling pathways[55,56,57].

Alterations and prevalence: Recurrent activating mutations differentially activate mTORC1 or mTORC2 leading to either S6K1/4EBP1 or AKT1 phosphorylation, respectively[150]. Somatic mutations in MTOR are observed in 12% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, 8% of kidney renal clear cell carcinoma and colorectal adenocarcinoma, 7% of stomach adenocarcinoma, 5% of lung adenocarcinoma, 4% of esophageal adenocarcinoma and lung squamous cell carcinoma, 3% of bladder urothelial carcinoma, kidney chromophobe, and cervical squamous cell carcinoma, and 2% of liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, head and neck squamous cell carcinoma, pancreatic adenocarcinoma, thymoma, glioblastoma multiforme, and acute myeloid leukemia[5,6]. MTOR amplification is observed in 2% of ovarian serous cystadenocarcinoma, sarcoma, and esophageal adenocarcinoma[5,6]. Alterations in MTOR are also observed in pediatric cancers[6]. Somatic mutations are observed in 12% of non-Hodgkin lymphoma (2 in 17 cases), 7% of Hodgkin lymphoma (4 in 61 cases), 5% of soft tissue sarcoma (2 in 38 cases) and T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases) and bone cancer (3 in 327 cases), and less than 1% of embryonal tumors (3 in 332 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), and Wilms tumor (1 in 710 cases)[6]. Amplification of MTOR is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[6].

Potential relevance: Two first generation MTOR inhibitors termed rapalogs (analogues of rapamycin) have been approved by the FDA: temsirolimus[151] (2007) for the treatment of renal cell carcinoma (RCC) and everolimus[152] (2009) for the treatment of breast, pancreatic, gastrointestinal, and lung cancers, RCC, and subependymal giant cell astrocytomas. Mutations in the FRB domain of mTOR are a potential mechanism of acquired resistance to first generation rapalogs[56,153]. While first-generation rapalogs form inhibitory complexes with FKBP-12, second generation mTOR inhibitors such as PF-04691502 and gedatolisib target the mTOR kinase domain directly[154].

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[155]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[156,157]. 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[158]. 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[159]. 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)[159]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[160,161,162,163,164]. 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[157]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[156,157,161,165].

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[156,157,166,167]. 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[166,167].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[168] (2014) and nivolumab[169] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[168] 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-

Biomarker Descriptions (continued)

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[168]. Dostarlimab[170] (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[162,171]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[172] (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[162,173,174]. 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[174]. 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[175,176]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[175,176].

PBRM1 p.(R1160*) c.3478C>T

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[48]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[48,49]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[48,50]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[51,52].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[5,6]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[108]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[109]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[110]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[39,92]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[111]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[112].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[5,6]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[112].

Potential relevance: The PARP inhibitor, olaparib[26] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[34], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RICTOR p.(E643K) c.1927G>A

RPTOR independent companion of MTOR complex 2

Background: The RICTOR gene encodes the RPTOR independent companion of MTOR complex 2, a core component of the mTOR complex-2 (mTORC2)[1,53]. RICTOR complexes with MTOR, DEPTOR, mSin1 and Protor1/2 to form the mTORC2 complex, which regulates cell proliferation and survival by phosphorylating members of the PKA/PKG/PKC family of protein kinases[54]. The mTORC2 complex is a downstream effector of the PI3K/AKT/MTOR signaling pathway and facilitates integration of the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK signaling pathways[55,56,57]. Independent of mTORC2, RICTOR can interact with integrin-linked kinases and promote

Biomarker Descriptions (continued)

phosphorylation of AKT[54,58]. Aberrations in RICTOR can lead to downstream pathway activation promoting cell proliferation and survival, supporting an oncogenic role for RICTOR[59].

Alterations and prevalence: Amplification of RICTOR is observed in several types of solid tumors and has been observed to correlate with protein overexpression[60]. Specifically, RICTOR amplification is observed in 10% of lung squamous cell carcinoma, 8% of esophageal adenocarcinoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% of adrenocortical carcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, ovarian serous cystadenocarcinoma, and sarcoma[5,6]. Somatic mutations in RICTOR are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, 5% of stomach adenocarcinoma and bladder urothelial carcinoma, and 3% of lung adenocarcinoma and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for RICTOR aberrations. RICTOR overexpression is associated with poor survival in hepatocellular carcinoma and endometrial carcinoma[61,62].

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[82]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[83]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[84,85,86]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[87].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of HLA-A is observed in 4% of DLBCL[5,6].

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

CSMD3 p.(R2442*) c.7324C>T

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 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.

LARP4B p.(R716Q) c.2147G>A

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[7]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[7]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[8].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

MGA p.(R1155*) c.3463C>T

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[1,113]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[114]. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation[113]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[115]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[116].

Alterations and prevalence: Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma[5,6]. MGA biallelic deletion is observed in 6% of diffuse large B-cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy[116].

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[63]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[63,64]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[65,66,67].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[5,6]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[5,6,68]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[68].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

SRC amplification

SRC proto-oncogene, non-receptor tyrosine kinase

Background: The SRC gene encodes the SRC proto-oncogene, non-receptor tyrosine kinase[1]. SRC belongs to the Src family that also includes proteins Fgr, Yes, Fyd, Lck, Hck, Lyn, and Blk[1,119]. SRC interacts with transmembrane receptor tyrosine kinases (RTKs), including EGFR, HER2, PDGFR, IGF-1R, and HGFR, to directly transduce extracellular signals from these receptors to downstream effector molecules such as PI3Ks, AKT, and STAT3[120]. SRC is known be critical in tumor progression and metastasis due to its impact in the regulation of cell migration, adhesion, invasion, and stabilization of focal adhesion complexes[120]. Specifically, interaction of SRC with the EGF receptor family members, including EGFR and HER2, has been shown to promote cell survival and tumorigenesis, supporting an oncogenic role for SRC[121].

Alterations and prevalence: Somatic mutations in SRC are observed in 2% of melanoma, and 1% of uterine and bladder cancer[5,6]. Amplifications are observed in 7% of colorectal cancer, and 2-3% of uterine, stomach, and esophageal cancer[5,6]. Overexpression of SRC and its kinase activity has been reported in lung, neural, ovarian, esophageal, and gastric cancer[122].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for SRC aberrations. Dasatinib is a tyrosine kinase inhibitor targeting SRC that is FDA approved for use in chronic myeloid leukemia or Philadelphia-chromosome positive acute lymphocytic leukemia[123].

PLCG1 amplification

phospholipase C gamma 1

Background: The PLCG1 gene encodes phospholipase C gamma 1, one of 13 phospholipase C (PLC) isozymes, that catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate the second messenger molecules, inositol 1,4,5-trisphosphate and diacylglycerol[1,78]. PLCG1 interacts with several signaling molecules, including phosphoinositide-dependent kinase 1 (PDK1) and AKT[79,80]. PLCG1 has also been implicated in the regulation of mitogen-mediated signaling cascades, including the RAS/RAF/MEK/ERK pathway, and positively regulates several cellular and physiological functions including cell proliferation, migration/invasion and angiogenesis[79,80,81]. Overexpression of PLCG1 has been found in many cancers, including head and neck cancer, breast cancer, pancreatic cancer, and colon cancer, and is associated with tumor growth and progression[79].

Alterations and prevalence: Somatic mutations in PLCG1 are predominantly missense and observed in 5% of uterine corpus endometrial carcinoma, skin cutaneous melanoma, and stomach adenocarcinoma, 3% of adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, and cholangiocarcinoma, and 2% of sarcoma, head and neck squamous cell carcinoma, lung adenocarcinoma, cervical squamous cell carcinoma, diffuse large B-cell lymphoma, liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[5,6]. Amplification of PLCG1 is observed in about 7% of colorectal adenocarcinoma, 5% of uterine carcinosarcoma, 4% of stomach adenocarcinoma, 3% of adrenocortical carcinoma, and 2% of esophageal adenocarcinoma and sarcoma[5,6]

Potential relevance: Currently, no therapies are approved for PLCG1 aberrations.

AMER1 p.(R531*) c.1591C>T

APC membrane recruitment protein 1

Background: The AMER1 gene encodes APC membrane recruitment protein 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,69]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[70,71]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[71]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[72]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[69].

Alterations and prevalence: Somatic mutations of AMER1 are observed in 13% of colorectal adenocarcinoma,10% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 4% of stomach adenocarcinoma, and uterine carcinosarcoma, 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and breast invasive carcinoma[5,6]. Biallelic deletion of AMER1 is observed in 2% of esophageal adenocarcinoma, diffuse large b-cell lymphoma, uterine carcinosarcoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma, and 1% of stomach adenocarcinoma, sarcoma, liver hepatocellular carcinoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for AMER1 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,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, 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

BRCA2 deletion

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

ATM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
senaparib, IMP-9064	✖	✖	✖	✖	● (I/II)

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
zotatifin, hormone therapy	✖	✖	✖	✖	● (I/II)

ATM p.(R248*) c.742C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)
tuvusertib, PL-0264	✖	✖	✖	✖	● (I)

BARD1 deletion

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

CHEK1 deletion

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

FGF19 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TYRA-430	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***23.43%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
BARD1	***CNV, CN:1.0***
BARD1	***LOH, 2q35(215593375-215674382)x1***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)x1***

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

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

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Lu et al. CSMD3 is Associated with Tumor Mutation Burden and Immune Infiltration in Ovarian Cancer Patients. Int J Gen Med. 2021;14:7647-7657. PMID: 34764678
3. Lau et al. Identification of two new members of the CSMD gene family. Genomics. 2003 Sep;82(3):412-5. PMID: 12906867
4. Cai et al. Epigenetic alterations are associated with tumor mutation burden in non-small cell lung cancer. J Immunother Cancer. 2019 Jul 26;7(1):198. PMID: 31349879
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
6. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
7. Seetharaman et al. The RNA-binding protein LARP4 regulates cancer cell migration and invasion. Cytoskeleton (Hoboken). 2016 Nov;73(11):680-690. PMID: 27615744
8. Koso et al. Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma. Cancer Res. 2016 Apr 15;76(8):2254-64. PMID: 26933087
9. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553
10. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514
11. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
12. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J. Natl. Cancer Inst. 2007 Dec 5;99(23):1811-4. PMID: 18042939
13. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
14. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. JNCI Cancer Spectr. 2020 Aug;4(4):pkaa029. PMID: 32676552
15. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
16. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin. Proc. 2010 Dec;85(12):1111-20. PMID: 21123638
17. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U.S.A. 2011 Nov 1;108(44):18032-7. PMID: 22006311
18. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J. Clin. Oncol. 2012 Jul 20;30(21):2654-63. PMID: 22711857
19. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol. Biomarkers Prev. 2004 Dec;13(12):2078-83. PMID: 15598764
20. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434
21. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br. J. Cancer. 2000 Nov;83(10):1301-8. PMID: 11044354
22. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589
23. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br. J. Cancer. 2018 Nov;119(11):1401-1409. PMID: 30353044
24. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913-7. PMID: 15829966
25. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PMID: 15829967
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
28. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf

References (continued)

29. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
31. https://www.jnj.com/media-center/press-releases/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-niraparib-for-the-treatment-of-metastatic-castration-resistant-prostate-cancer
32. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013 Feb;229(3):422-9. PMID: 23165508
33. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
34. https://www.senhwabio.com//en/news/20220125
35. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047
36. Rodríguez et al. Fanconi anemia pathway. Curr Biol. 2017 Sep 25;27(18):R986-R988. PMID: 28950089
37. Garcia-Higuera et al. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol. Cell. 2001 Feb;7(2):249-62. PMID: 11239454
38. Hussain et al. Direct interaction of FANCD2 with BRCA2 in DNA damage response pathways. Hum. Mol. Genet. 2004 Jun 15;13(12):1241-8. PMID: 15115758
39. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
40. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
41. Michl et al. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. EMBO J. 2016 May 2;35(9):909-23. PMID: 27037238
42. Abbasi et al. A rare FANCA gene variation as a breast cancer susceptibility allele in an Iranian population. Mol Med Rep. 2017 Jun;15(6):3983-3988. PMID: 28440412
43. Levran et al. Sequence variation in the Fanconi anemia gene FAA. Proc. Natl. Acad. Sci. U.S.A. 1997 Nov 25;94(24):13051-6. PMID: 9371798
44. Antonio Casado et al. A comprehensive strategy for the subtyping of patients with Fanconi anaemia: conclusions from the Spanish Fanconi Anemia Research Network. J. Med. Genet. 2007 Apr;44(4):241-9. PMID: 17105750
45. Tischkowitz et al. Deletion and reduced expression of the Fanconi anemia FANCA gene in sporadic acute myeloid leukemia. Leukemia. 2004 Mar;18(3):420-5. PMID: 14749703
46. McCabe et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res. 2006 Aug 15;66(16):8109-15. PMID: 16912188
47. Wilkes et al. A germline FANCA alteration that is associated with increased sensitivity to DNA damaging agents. Cold Spring Harb Mol Case Stud. 2017 Sep;3(5). PMID: 28864460
48. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
49. Hodges et al. The Many Roles of BAF (mSWI/SNF) and PBAF Complexes in Cancer. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8). PMID: 27413115
50. Thompson. Polybromo-1: the chromatin targeting subunit of the PBAF complex. Biochimie. 2009 Mar;91(3):309-19. PMID: 19084573
51. Hopson et al. BAF180: Its Roles in DNA Repair and Consequences in Cancer. ACS Chem Biol. 2017 Oct 20;12(10):2482-2490. PMID: 28921948
52. Carril-Ajuria et al. Cancers (Basel). 2019 Dec 19;12(1). PMID: 31861590
53. Sparks et al. Targeting mTOR: prospects for mTOR complex 2 inhibitors in cancer therapy. Oncogene. 2010 Jul 1;29(26):3733-44. PMID: 20418915
54. Saxton et al. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017 Mar 9;168(6):960-976. PMID: 28283069
55. Pópulo et al. The mTOR signalling pathway in human cancer. Int J Mol Sci. 2012;13(2):1886-918. PMID: 22408430
56. Faes et al. Resistance to mTORC1 Inhibitors in Cancer Therapy: From Kinase Mutations to Intratumoral Heterogeneity of Kinase Activity. Oxid Med Cell Longev. 2017;2017:1726078. Epub 2017 Feb 9. PMID: 28280521
57. Mendoza et al. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem. Sci. 2011 Jun;36(6):320-8. PMID: 21531565
58. Hua et al. Targeting mTOR for cancer therapy. J Hematol Oncol. 2019 Jul 5;12(1):71. PMID: 31277692
59. Jebali et al. The role of RICTOR downstream of receptor tyrosine kinase in cancers. Mol Cancer. 2018 Feb 19;17(1):39. PMID: 29455662
60. Bang et al. Correlation between RICTOR overexpression and amplification in advanced solid tumors. PMID: 31740232

References (continued)

61. Kaibori et al. Influence of Rictor and Raptor Expression of mTOR Signaling on Long-Term Outcomes of Patients with Hepatocellular Carcinoma. Dig. Dis. Sci. 2015 Apr;60(4):919-28. PMID: 25371154
62. Wen et al. Rictor is an independent prognostic factor for endometrial carcinoma. Int J Clin Exp Pathol. 2014;7(5):2068-78. PMID: 24966915
63. Cheng et al. G protein pathway suppressor 2 (GPS2) is a transcriptional corepressor important for estrogen receptor alpha-mediated transcriptional regulation. J Biol Chem. 2009 Dec 25;284(52):36395-36404. PMID: 19858209
64. Si et al. G protein pathway suppressor 2 suppresses gastric cancer by destabilizing epidermal growth factor receptor. Cancer Sci. 2021 Dec;112(12):4867-4882. PMID: 34609770
65. Bien-Willner et al. Mutation and expression analysis in medulloblastoma yields prognostic variants and a putative mechanism of disease for i17q tumors. Acta Neuropathol Commun. 2014 Jul 17;2:74. PMID: 25030029
66. Huang et al. G protein pathway suppressor 2 (GPS2) acts as a tumor suppressor in liposarcoma. Tumour Biol. 2016 Oct;37(10):13333-13343. PMID: 27460081
67. Chan et al. Loss of G-Protein Pathway Suppressor 2 Promotes Tumor Growth Through Activation of AKT Signaling. Front Cell Dev Biol. 2020;8:608044. PMID: 33490071
68. O'Meara et al. Identification of an MLL4-GPS2 fusion as an oncogenic driver of undifferentiated spindle cell sarcoma in a child. Genes Chromosomes Cancer. 2014 Dec;53(12):991-8. PMID: 25139254
69. Liu et al. Aging (Albany NY). 2020 May 4;12(9):8372-8396. PMID: 32365332
70. Komiya et al. Wnt signal transduction pathways. Organogenesis. 2008 Apr;4(2):68-75. PMID: 19279717
71. Zhang et al. J Hematol Oncol. 2020 Dec 4;13(1):165. PMID: 33276800
72. Rivera et al. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. Science. 2007 Feb 2;315(5812):642-5. PMID: 17204608
73. Patil et al. Checkpoint kinase 1 in DNA damage response and cell cycle regulation. Cell. Mol. Life Sci. 2013 Nov;70(21):4009-21. PMID: 23508805
74. Bartek et al. Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell. 2003 May;3(5):421-9. PMID: 12781359
75. Huang et al. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. Mol. Cancer Ther. 2008 Jun;7(6):1440-9. PMID: 18566216
76. Zhang et al. Roles of Chk1 in cell biology and cancer therapy. Int. J. Cancer. 2014 Mar 1;134(5):1013-23. PMID: 23613359
77. Sen et al. CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. Cancer Res. 2017 Jul 15;77(14):3870-3884. PMID: 28490518
78. Hajicek et al. Structural basis for the activation of PLC-γ isozymes by phosphorylation and cancer-associated mutations. Elife. 2019 Dec 31;8. PMID: 31889510
79. Mandal et al. Recent advances in understanding the molecular role of phosphoinositide-specific phospholipase C gamma 1 as an emerging onco-driver and novel therapeutic target in human carcinogenesis. Biochim Biophys Acta Rev Cancer. 2021 Dec;1876(2):188619. PMID: 34454048
80. Jang et al. PLCγ1: Potential arbitrator of cancer progression. Adv Biol Regul. 2018 Jan;67:179-189. PMID: 29174396
81. Li et al. Phospholipase Cγ1 (PLCG1) overexpression is associated with tumor growth and poor survival in IDH wild-type lower-grade gliomas in adult patients. Lab Invest. 2022 Feb;102(2):143-153. PMID: 34697421
82. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
83. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204
84. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
85. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
86. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
87. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675
88. Maréchal et al. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol. 2013 Sep 1;5(9). PMID: 24003211
89. Matsuoka et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007 May 25;316(5828):1160-6. PMID: 17525332

References (continued)

90. Ditch et al. The ATM protein kinase and cellular redox signaling: beyond the DNA damage response. Trends Biochem. Sci. 2012 Jan;37(1):15-22. PMID: 22079189
91. Kozlov et al. Autophosphorylation and ATM activation: additional sites add to the complexity. J. Biol. Chem. 2011 Mar 18;286(11):9107-19. PMID: 21149446
92. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. Endocr. Relat. Cancer. 2016 Jun;23(6):R267-85. PMID: 27226207
93. Cynthia et al. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016 Nov 25;11(1):159. PMID: 27884168
94. Gilardini Montani et al. ATM-depletion in breast cancer cells confers sensitivity to PARP inhibition. CR. PMID: 24252502
95. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin. Cancer Res. 2014 Feb 1;20(3):764-75. PMID: 24240112
96. Mateo et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N. Engl. J. Med. 2015 Oct 29;373(18):1697-708. PMID: 26510020
97. Naqvi et al. Heterogeneity of the Treatment Effect with PARP Inhibitors in Metastatic Castration-resistant Prostate Cancer: A Living Interactive Systematic Review and Meta-analysis. Eur Urol. 2025 Jun;87(6):626-640. PMID: 39848867
98. Evans et al. Exploring the Impact of Treatment Switching on Overall Survival from the PROfound Study in Homologous Recombination Repair (HRR)-Mutated Metastatic Castration-Resistant Prostate Cancer (mCRPC). Target Oncol. 2021 Sep;16(5):613-623. PMID: 34478046
99. Beenken et al. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov. 2009 Mar;8(3):235-53. PMID: 19247306
100. Ornitz et al. The Fibroblast Growth Factor signaling pathway. Wiley Interdiscip Rev Dev Biol . May-Jun 2015;4(3):215-66. doi: 10.1002/wdev.176. PMID: 25772309
101. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer. 2017 May;17(5):318-332. PMID: 28303906
102. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. Biochim. Biophys. Acta. 2012 Apr;1823(4):850-60. PMID: 22273505
103. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. Nat Commun. 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
104. Itoh et al. Evolution of the Fgf and Fgfr gene families. Trends Genet. 2004 Nov;20(11):563-9. PMID: 15475116
105. Mathieu et al. Receptor binding and mitogenic properties of mouse fibroblast growth factor 3. Modulation of response by heparin. J. Biol. Chem. 1995 Oct 13;270(41):24197-203. PMID: 7592624
106. Tai et al. Co-overexpression of fibroblast growth factor 3 and epidermal growth factor receptor is correlated with the development of nonsmall cell lung carcinoma. Cancer. 2006 Jan 1;106(1):146-55. PMID: 16329133
107. Hu et al. Up-regulation of fibroblast growth factor 3 is associated with tumor metastasis and recurrence in human hepatocellular carcinoma. Cancer Lett. 2007 Jul 8;252(1):36-42. PMID: 17215076
108. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. Genes (Basel). 2018 Dec 13;9(12). PMID: 30551670
109. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. Semin. Cell Dev. Biol. 2011 Oct;22(8):898-905. PMID: 21821141
110. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. Mol. Cell. Biol. 2013 Jan;33(2):387-95. PMID: 23149936
111. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. Cancer Res. 2006 Jun 15;66(12):6018-24. PMID: 16778173
112. Pelttari et al. RAD51B in Familial Breast Cancer. PLoS ONE. 2016;11(5):e0153788. PMID: 27149063
113. Hurlin et al. The MAX-interacting transcription factor network. Semin. Cancer Biol. 2006 Aug;16(4):265-74. PMID: 16908182
114. Susan. An Overview of the Basic Helix-Loop-Helix Proteins. Genome Biol. 2004;5(6):226. PMID: 15186484
115. Llabata et al. Multi-Omics Analysis Identifies MGA as a Negative Regulator of the MYC Pathway in Lung Adenocarcinoma. Mol Cancer Res. 2020 Apr;18(4):574-584. PMID: 31862696
116. Sun et al. MGA Mutation as a Novel Biomarker for Immune Checkpoint Therapies in Non-Squamous Non-Small Cell Lung Cancer. Front Pharmacol. 2021;12:625593. PMID: 33927616
117. Marteijn et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014 Jul;15(7):465-81. PMID: 24954209
118. Natale et al. Xeroderma pigmentosum-Cockayne syndrome complex. Orphanet J Rare Dis. 2017 Apr 4;12(1):65. PMID: 28376890

References (continued)

119. Shen et al. The Src family kinase Fgr is a transforming oncoprotein that functions independently of SH3-SH2 domain regulation. Sci Signal. 2018 Oct 23;11(553). PMID: 30352950
120. Zhang et al. Targeting Src family kinases in anti-cancer therapies: turning promise into triumph. Trends Pharmacol Sci. 2012 Mar;33(3):122-8. PMID: 22153719
121. Biscardi et al. Tyrosine kinase signalling in breast cancer: epidermal growth factor receptor and c-Src interactions in breast cancer. Breast Cancer Res. 2000;2(3):203-10. PMID: 11250711
122. Irby et al. Role of Src expression and activation in human cancer. Oncogene. 2000 Nov 20;19(49):5636-42. PMID: 11114744
123. Wheeler et al. The role of Src in solid tumors. Oncologist. 2009 Jul;14(7):667-78. PMID: 19581523
124. Morris et al. BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. Hum. Mol. Genet. 2004 Apr 15;13(8):807-17. PMID: 14976165
125. Baer et al. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity. Curr. Opin. Genet. Dev. 2002 Feb;12(1):86-91. PMID: 11790560
126. Zhao et al. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. Nature. 2017 Oct 19;550(7676):360-365. PMID: 28976962
127. Cimmino et al. Dualistic Role of BARD1 in Cancer. Genes (Basel). 2017 Dec 8;8(12). PMID: 29292755
128. De Summa et al. BRCAness: a deeper insight into basal-like breast tumors. Ann. Oncol. 2013 Nov;24 Suppl 8:viii13-viii21. PMID: 24131964
129. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015 Apr 1;7(4):a016600. PMID: 25833843
130. Irminger-Finger et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. Mol. Cell. 2001 Dec;8(6):1255-66. PMID: 11779501
131. Thai et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. Hum. Mol. Genet. 1998 Feb;7(2):195-202. PMID: 9425226
132. Repana et al. Targeting FGF19/FGFR4 Pathway: A Novel Therapeutic Strategy for Hepatocellular Carcinoma. Diseases. 2015 Oct 28;3(4):294-305. PMID: 28943626
133. Goetz et al. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Mol. Cell. Biol. 2007 May;27(9):3417-28. PMID: 17339340
134. Lu et al. Fibroblast Growth Factor Receptor 4 (FGFR4) Selective Inhibitors as Hepatocellular Carcinoma Therapy: Advances and Prospects. J. Med. Chem. 2018 Nov 16. PMID: 30403487
135. Miura et al. Fibroblast growth factor 19 expression correlates with tumor progression and poorer prognosis of hepatocellular carcinoma. BMC Cancer. 2012 Feb 6;12:56. doi: 10.1186/1471-2407-12-56. PMID: 22309595
136. Kiuru-Kuhlefelt et al. FGF4 and INT2 oncogenes are amplified and expressed in Kaposi's sarcoma. Mod Pathol. 2000 Apr;13(4):433-7. PMID: 10786811
137. Suzuki et al. Predominant expression of fibroblast growth factor (FGF) 8, FGF4, and FGF receptor 1 in nonseminomatous and highly proliferative components of testicular germ cell tumors. Virchows Arch. 2001 Nov;439(5):616-21. PMID: 11764380
138. Yeh et al. FBXW7: a critical tumor suppressor of human cancers. Mol Cancer. 2018 Aug 7;17(1):115. doi: 10.1186/s12943-018-0857-2. PMID: 30086763
139. Wang et al. Tumor suppressor functions of FBW7 in cancer development and progression. FEBS Lett. 2012 May 21;586(10):1409-18. PMID: 22673505
140. Uhlén et al. Proteomics. Tissue-based map of the human proteome. Science. 2015 Jan 23;347(6220):1260419. doi: 10.1126/science.1260419. PMID: 25613900
141. Yada et al. Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7. EMBO J. 2004 May 19;23(10):2116-25. PMID: 15103331
142. Hori et al. Notch signaling at a glance. J. Cell. Sci. 2013 May 15;126(Pt 10):2135-40. PMID: 23729744
143. Aydin et al. FBXW7 mutations in melanoma and a new therapeutic paradigm. J. Natl. Cancer Inst. 2014 Jun;106(6):dju107. PMID: 24838835
144. Jardim et al. FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS ONE. 2014;9(2):e89388. PMID: 24586741
145. Korphaisarn et al. FBXW7 missense mutation: a novel negative prognostic factor in metastatic colorectal adenocarcinoma. Oncotarget. 2017 Jun 13;8(24):39268-39279. PMID: 28424412

References (continued)

146. Donna M et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
147. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
148. https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda
149. Villaruz et al. Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation. Lung Cancer. 2014 Feb;83(2):300-1. PMID: 24360397
150. Grabiner et al. A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin sensitivity. Cancer Discov. 2014 May;4(5):554-63. PMID: 24631838
151. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022088s021s023lbl.pdf
152. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203985s023,022334s051lbl.pdf
153. Rodrik-Outmezguine et al. Overcoming mTOR resistance mutations with a new-generation mTOR inhibitor. Nature. 2016 Jun 9;534(7606):272-6. PMID: 27279227
154. Del Campo et al. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol. Oncol. 2016 Jul;142(1):62-69. PMID: 27103175
155. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
156. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. Front Oncol. 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
157. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
158. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. Front Microbiol. 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
159. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57. PMID: 9823339
160. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. Cancer Res. 2002 Jan 1;62(1):53-7. PMID: 11782358
161. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
162. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
163. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
164. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. Medicine (Baltimore). 2015 Dec;94(50):e2260. PMID: 26683947
165. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. J. Clin. Oncol. 2019 Feb 1;37(4):286-295. PMID: 30376427
166. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. Nat Commun. 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
167. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
168. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
169. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
170. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
171. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
172. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
173. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N. Engl. J. Med. 2003 Jul 17;349(3):247-57. PMID: 12867608
174. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann. Oncol. 2015 Jan;26(1):126-32. PMID: 25361982
175. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
176. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031

References (continued)

177. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
178. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
179. Ding et al. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms: A systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):2717-2729. PMID: 30950241
180. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
181. Shan et al. Cyclin D1 overexpression correlates with poor tumor differentiation and prognosis in gastric cancer. Oncol Lett. 2017 Oct;14(4):4517-4526. PMID: 28943959
182. Cancer Genome Atlas Research et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. PMID: 23636398
183. Beà et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. Proc. Natl. Acad. Sci. U.S.A. 2013 Nov 5;110(45):18250-5. PMID: 24145436
184. Diehl et al. Glycogen synthase kinase-3beta regulates cyclin D1 proteolysis and subcellular localization. Genes Dev. 1998 Nov 15;12(22):3499-511. PMID: 9832503
185. Alt et al. Phosphorylation-dependent regulation of cyclin D1 nuclear export and cyclin D1-dependent cellular transformation. Genes Dev. 2000 Dec 15;14(24):3102-14. PMID: 11124803
186. Moreno-Bueno et al. Cyclin D1 gene (CCND1) mutations in endometrial cancer. Oncogene. 2003 Sep 4;22(38):6115-8. PMID: 12955092
187. Benzeno et al. Identification of mutations that disrupt phosphorylation-dependent nuclear export of cyclin D1. Oncogene. 2006 Oct 12;25(47):6291-303. PMID: 16732330
188. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
189. Kim et al. Nuclear cyclin D1: an oncogenic driver in human cancer. J. Cell. Physiol. 2009 Aug;220(2):292-6. PMID: 19415697
190. Jares et al. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat. Rev. Cancer. 2007 Oct;7(10):750-62. PMID: 17891190
191. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]