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

Patient Name: 송민경
Gender: F
Sample ID: N25-312

Primary Tumor Site:
Collection Date: 2021.06.30

Sample Cancer Type: Breast Cancer

Report Highlights
6 Relevant Biomarkers
10 Therapies Available
29 Clinical Trials

Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***12.47 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*ESR1 p.(D538G) c.1613A>G* estrogen receptor 1 Allele Frequency: 44.04% Locus: chr6:152419926 Transcript: NM_001122740.2	**elacestrant** [1, 2 / I, II+]	None*	0
IA	*BRCA2 p.(T1346Sfs*5) c.4037_4038delCT* BRCA2, DNA repair associated Allele Frequency: 62.86% Locus: chr13:32912528 Transcript: NM_000059.4	olaparib [II+] talazoparib [II+]	**abiraterone + niraparib** [1, 2 / II+] **bevacizumab + olaparib** [1, 2 / II+] **niraparib** [1 / II+] **olaparib** [1, 2 / II+] **rucaparib** [1 / II+] **talazoparib + hormone therapy** [1 / II+] bevacizumab + niraparib [II+] olaparib + hormone therapy	25
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	4

*** 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	*ATR p.(R2001*) c.6001C>T* ATR serine/threonine kinase Allele Frequency: 3.27% Locus: chr3:142212051 Transcript: NM_001184.4	None*	None*	1
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	*LATS1 p.(L85Afs*6) c.253_254delCT* large tumor suppressor kinase 1 Allele Frequency: 42.55% Locus: chr6:150023008 Transcript: NM_004690.4	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*APC p.(Y622Gfs*7) c.1863_1866delTTAC, ARID1B deletion, LATS1 deletion, LATS2 deletion, MAP2K4 p.(R281*) c.841C>T, MAPK1 amplification, MLH1 c.677+3A>G, MSH6 p.(K1358Dfs*2) c.4068_4071dup, PARP4 deletion, RNASEH2B deletion, SMAD4 p.(L533P) c.1598T>C, TCF7L2 deletion, UGT1A1 p.(G71R) c.211G>A, TGFBR2 deletion, TGFBR2 p.(R485C) c.1453C>T, HLA-A p.(L180*) c.539T>A, PRDM1 deletion, HDAC2 deletion, MAP3K4 deletion, GATA3 p.(D336Gfs*17) c.1006_1007insG, SUFU deletion, ETV6 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ESR1	p.(D538G)	c.1613A>G	COSM94250	chr6:152419926	44.04%	NM_001122740.2	missense
BRCA2	p.(T1346Sfs*5)	c.4037_4038delCT	.	chr13:32912528	62.86%	NM_000059.4	frameshift Deletion
ATR	p.(R2001*)	c.6001C>T	.	chr3:142212051	3.27%	NM_001184.4	nonsense
LATS1	p.(L85Afs*6)	c.253_254delCT	.	chr6:150023008	42.55%	NM_004690.4	frameshift Deletion
APC	p.(Y622Gfs*7)	c.1863_1866delTTAC	.	chr5:112170766	26.87%	NM_000038.6	frameshift Deletion
MAP2K4	p.(R281*)	c.841C>T	.	chr17:12028638	3.23%	NM_003010.4	nonsense
MLH1	p.(?)	c.677+3A>G	VCV000090315	chr3:37053593	44.10%	NM_000249.4	unknown
MSH6	p.(K1358Dfs*2)	c.4068_4071dup	.	chr2:48033981	39.09%	NM_000179.3	frameshift Insertion
SMAD4	p.(L533P)	c.1598T>C	.	chr18:48604776	59.49%	NM_005359.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.43%	NM_000463.3	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TGFBR2	p.(R485C)	c.1453C>T	.	chr3:30715720	3.80%	NM_001024847.2	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	98.79%	NM_001242758.1	nonsense
GATA3	p.(D336Gfs*17)	c.1006_1007insG	COSM41681	chr10:8111513	30.66%	NM_001002295.2	frameshift Insertion
ERRFI1	p.(I65M)	c.195A>G	.	chr1:8075375	58.05%	NM_018948.4	missense
CHIA	p.(D343N)	c.1027G>A	.	chr1:111861853	3.18%	NM_201653.4	missense
NOTCH2	p.(N986D)	c.2956A>G	.	chr1:120484174	3.41%	NM_024408.4	missense
OR2T4	p.([S262L;A263V])	c.785_788delCAGCinsTAGT	.	chr1:248525667	4.25%	NM_001004696.1	missense, missense
STAT1	p.(D234G)	c.701A>G	.	chr2:191862666	2.79%	NM_007315.4	missense
CUL3	p.(R148Q)	c.443G>A	.	chr2:225379425	4.14%	NM_003590.5	missense
PDCD1	p.(?)	c.627+1G>A	.	chr2:242794100	5.32%	NM_005018.3	unknown
CNTN6	p.(A805T)	c.2413G>A	.	chr3:1424988	22.24%	NM_014461.4	missense
PP2D1	p.(A268V)	c.803C>T	.	chr3:20042809	25.48%	NM_001252657.2	missense
ARHGEF38	p.(D442Y)	c.1324G>T	.	chr4:106580301	27.32%	NM_001242729.2	missense
FAT1	p.(P406L)	c.1217C>T	.	chr4:187629765	3.30%	NM_005245.4	missense
FLT4	p.(L401M)	c.1201C>A	.	chr5:180053168	16.76%	NM_182925.5	missense
KMT2C	p.(P1463S)	c.4387C>T	.	chr7:151891645	3.69%	NM_170606.3	missense
TSC1	p.(R706H)	c.2117G>A	.	chr9:135779129	2.53%	NM_000368.5	missense
CCND1	p.(M202L)	c.604A>C	.	chr11:69462791	17.84%	NM_053056.3	missense
YAP1	p.(A228T)	c.682G>A	.	chr11:102033296	2.72%	NM_001130145.3	missense
EXPH5	p.(M1?)	c.3G>A	.	chr11:108464261	2.97%	NM_015065.3	missense
KMT2D	p.(L3931F)	c.11791C>T	.	chr12:49426697	21.01%	NM_003482.4	missense
RB1	p.(P238S)	c.712C>T	.	chr13:48934257	3.25%	NM_000321.3	missense
TJP1	p.(G781D)	c.2342G>A	.	chr15:30018653	3.74%	NM_003257.5	missense
CSNK1G1	p.(R134*)	c.400C>T	.	chr15:64508805	2.97%	NM_022048.5	nonsense
ZFHX3	p.(E1812K)	c.5434G>A	.	chr16:72831147	2.64%	NM_006885.4	missense
NCOR1	p.(K204R)	c.611A>G	.	chr17:16068300	5.95%	NM_006311.4	missense
DSC1	p.(E233A)	c.698A>C	.	chr18:28728535	3.79%	NM_024421.2	missense
BCL2	p.(R106C)	c.316C>T	.	chr18:60985584	22.71%	NM_000633.3	missense
MEF2B	p.(P277S)	c.829C>T	.	chr19:19257134	3.89%	NM_001145785.2	missense
ZRSR2	p.(S188L)	c.563C>T	.	chrX:15833805	3.23%	NM_005089.4	missense
BCOR	p.(E1732K)	c.5194G>A	.	chrX:39911436	2.92%	NM_001123385.2	missense
BCOR	p.(A1471S)	c.4411G>T	.	chrX:39921409	44.29%	NM_001123385.2	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KDM6A	p.(A788V)	c.2363C>T	.	chrX:44929263	3.09%	NM_021140.3	missense
SLC9A7	p.(R634*)	c.1900C>T	.	chrX:46472753	5.08%	NM_001257291.2	nonsense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0	0.32
BAP1	chr3:52436290	0.45	0.69
ARID1B	chr6:157099057	0.43	0.68
LATS1	chr6:149982844	0.48	0.7
LATS2	chr13:21548922	0.28	0.65
MAPK1	chr22:22123473	8.32	2.26
PARP4	chr13:25000551	0.13	0.63
RNASEH2B	chr13:51484145	0.4	0.68
TCF7L2	chr10:114710485	0.15	0.63
TGFBR2	chr3:30648337	0.38	0.68
PRDM1	chr6:106534408	0.2	0.64
HDAC2	chr6:114262171	0	0.58
MAP3K4	chr6:161412931	0.48	0.7
SUFU	chr10:104263903	0.45	0.69
ETV6	chr12:11803059	0.48	0.7
FGFR2	chr10:123239426	0.43	0.69
FGF9	chr13:22245989	0	0.54
KDM5C	chrX:53221892	6.8	1.96
SMC1A	chrX:53406966	6.03	1.81
CUL4B	chrX:119660593	6.68	1.93
STAG2	chrX:123156472	4.55	1.51

Biomarker Descriptions

ESR1 p.(D538G) c.1613A>G

estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses. A related gene, ESR2, encodes the cognate ERβ protein. ERα is a ligand-activated transcription factor regulated by the hormone estrogen[192,193]. Estrogen binding to ERα results in receptor dimerization,

Biomarker Descriptions (continued)

nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[194].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[195,196,197,198]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[199,200,201,202,203].

Potential relevance: The FDA has approved elacestrant[204] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[205]. The FDA has also granted fast track designations to the following therapies: AC699[206] (2024) and lasofoxifene[207] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizaestrant[208] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[209] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[210] (1977), fulvestrant[211] (2002), letrozole[212] (1995), and exemestane[213] (2005) are FDA approved for ER-positive metastatic breast cancers[214,215]. Although ERα and ERβ positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[216,217,218].

BRCA2 p.(T1346Sfs*5) c.4037_4038delCT

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[7,8].

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 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 metastatic castration-resistant prostate cancer (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. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[31]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[32]. 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[33], 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.

Biomarker Descriptions (continued)

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[148]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[149,150,151]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[152]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,152,153]. CDKN2A aberrations commonly co-occur with CDKN2B[148]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[154]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[155,156].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[157]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[7,8]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[7,8]. Alterations in CDKN2A are also observed in pediatric cancers[8]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[8]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[8].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[51,158,159]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[160]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[161,162,163]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[164]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[165,166,167,168].

ATR p.(R2001*) c.6001C>T

ATR serine/threonine kinase

Background: The ATR gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATM and PRKDC (also known as DNA-PKc)[128]. ATR and ATM act as master regulators of DNA damage response. Specifically, ATR and it's interacting protein ATRIP are involved in single-stranded DNA (ssDNA) repair while ATM is involved in double-stranded break (DSB) repair[129]. ATR is characterized as a tumor suppressor that plays a key role in maintaining genomic stability[130]. Upon activation, ATR phosphorylates downstream cell cycle and DNA damage signaling proteins such as CHK1, RAD17, RAD9, and BRCA1[131,132]. Germline mutations in ATR confer susceptibility to various cancers[133,134].

Alterations and prevalence: Somatic mutations of ATR are observed in 12% of melanoma, 11% of endometrial carcinoma, 8% of undifferentiated stomach adenocarcinoma and bladder urothelial carcinoma cases[7,8].

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 ATR.

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[174]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[174]. Germline mutations in

Biomarker Descriptions (continued)

BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[175,176,177,178,179,180].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[7,8]. BAP1 biallelic deletions are observed in 11% of mesothelioma[7,8].

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

LATS1 deletion, LATS1 p.(L85Afs*6) c.253_254delCT

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[1]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[34,35]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[36]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[36]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[37].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[7,8]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[7,8].

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

APC p.(Y622Gfs*7) c.1863_1866delTTAC

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[104]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[105,106]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[104,107]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[108].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[7,8,109]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[110,111].

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

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,169]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[169,170].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[170]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[170,171]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[169].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[171]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[7,8]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[7,8].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[172,173].

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2[1]. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members[34,35]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[36]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[36]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[37].

Alterations and prevalence: Somatic mutations in LATS2 are observed in 9% of mesothelioma, 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% stomach adenocarcinoma, and 3% of colorectal adenocarcinoma[7,8]. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for LATS2 aberrations.

MAP2K4 p.(R281*) c.841C>T

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[95]. Activation of MAPK proteins occurs through a kinase signaling cascade[95,96,97]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[95,96,97]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[95,96,97]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[98].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[7,8]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[7,8]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[99,100].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

MAPK1 amplification

mitogen-activated protein kinase 1

Background: The MAPK1 gene encodes the mitogen-activated protein kinase 1, also known as ERK2[1]. MAPK1 is involved in the ERK1/2 signaling pathway along with MAPK3, MAP2K2, MAP2K4, BRAF, and RAF1[95,219]. Activation of MAPK proteins occurs through a kinase signaling cascade[95,96,97]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[95,96,97]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[95,96,97]. MAPK1 activation leads to homodimerization and phosphorylation of downstream targets including transcription factors RSK, MSK, and MYC, cytoskeletal molecules, and nucleoporins[220]. MAPK1 mutations have been observed to confer gain of function and promote MAPK pathway signaling, supporting an oncogenic role for MAPK1[221,222].

Alterations and prevalence: Somatic mutations in MAPK1 are observed in up to 4% of cervical squamous cell carcinoma, and up to 2% of head and neck squamous cell and uterine corpus endometrial carcinomas[7,8]. The most common missense mutations occur at codon 322[7,8]. Amplifications in MAPK1 are observed in up to 4% of sarcoma, and 3% of bladder carcinoma, lung squamous carcinoma, and ovarian cancer[7,8].

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

Biomarker Descriptions (continued)

MLH1 c.677+3A>G

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[69]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[69,70]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[93,94]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[69]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[69]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[71]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[72,73,74]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[72,75]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[73,75,76,77]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[78,79,80,81].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[7,8]. Alterations in MLH1 are observed in pediatric cancers[7,8]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[7,8].

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 MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[82]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[83,84]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[85,86].

MSH6 p.(K1358Dfs*2) c.4068_4071dup

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[69]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[69]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication[69]. Mutations in MSH2 result in the degradation of MSH6[70]. MSH6, along with MLH1, MSH2, and PMS2, form the core components of the MMR pathway[69]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[69]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[71]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[72,73,74]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[72,75]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[73,75,76,77]. Specifically, MSH6 mutations are associated with an increased risk of ovarian and pancreatic cancer[78,79,80,81].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[7,8]. Alterations in MSH6 are observed in pediatric cancers[7,8]. Somatic mutations are observed in 9% of hepatobiliary cancer, 2% of T-lymphoblastic leukemia/lymphoma, 1% of B-lymphoblastic leukemia/lymphoma, and less than 1% of glioma (2 in 297 cases) and bone cancer (2 in 327 cases)[7,8].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[82]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[83,84]. MSH6 mutations are consistent with high grade in pediatric diffuse gliomas[85,86].

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[1]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[116]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis,

Biomarker Descriptions (continued)

nucleic acid metabolism, and regulation of chromatin structure[116,117]. PARP enzymes are involved in several DNA repair pathways[116,117]. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins[118].

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma[7,8]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[7,8].

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[119,120]. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. 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 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 BRCA1. Rucaparib[27] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[28] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. 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.

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[126,127]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[126]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[126].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[7,8]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[7,8].

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

SMAD4 p.(L533P) c.1598T>C

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[181,182]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[182,183,184]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[181,182]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[181]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[8,184,185]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[7,8,109].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[182,184,186,187,188]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[189,190]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[190]. In another clinical study of 173 newly diagnosed

Biomarker Descriptions (continued)

and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[191].

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,101]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[101,102,103]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[101]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[101].

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[7,8]. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma[7,8].

Potential relevance: Currently, no therapies are approved for TCF7L2 aberrations.

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,62]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[62,63]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[64]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[64,65,66,67]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[68].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[7,8].

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

TGFBR2 deletion, TGFBR2 p.(R485C) c.1453C>T

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[2]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[2]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[2]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[3]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[4,5,6].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[7,8]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

Biomarker Descriptions (continued)

HLA-A p.(L180*) c.539T>A

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[87]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[88]. 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[89,90,91]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[92].

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[7,8]. Biallelic loss of HLA-A is observed in 4% of DLBCL[7,8].

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

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[112,113,114]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[115]. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression[114]. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1[115].

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma[7,8]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[115]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[7,8].

Potential relevance: Currently, no therapies are approved for PRDM1 aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[140]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[140]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[140,141]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[140]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[140]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[140,142].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[7,8]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[7,8].

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[143]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[144]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[145]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[146].

Biomarker Descriptions (continued)

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[1]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[95]. Activation of MAPK proteins occurs through a kinase signaling cascade[95,96,97]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[95,96,97]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[95,96,97]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[147].

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[7,8]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[7,8].

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

GATA3 p.(D336Gfs*17) c.1006_1007insG

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,135,136]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[136]. GATA3 functions in the differentiation of immune cells and tissue development[137,138]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[137].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[7,8]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[7,8]. Alterations in GATA3 are also observed in the pediatric population[8]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[8]. Biallelic deletion is observed in 1% of peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[8].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[137,139].

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[121]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[122,123]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[124]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and are observed almost exclusively in children less than 3 years of age[125].

Alterations and prevalence: Somatic mutations are observed in 4% uterine corpus endometrial carcinoma and 2% esophageal adenocarcinoma and stomach adenocarcinoma[8]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[8]. Alterations in SUFU are also observed in pediatric cancers[8]. Somatic mutations in SUFU are observed in 1% of embryonal tumors (4 in 332 cases) and less than 1% of glioma (2 in 297 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[8]. Biallelic deletion of SUFU is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[8].

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

Biomarker Descriptions (continued)

ETV6 deletion

ETS variant 6

Background: The ETV6 gene encodes the E twenty-six (ETS) variant 1 transcription factor[38]. ETV6 contains an N-terminal pointed (PNT) domain responsible for protein-protein interactions and a C-terminal ETS domain involved in DNA binding[38]. ETV6 plays a critical role in embryonic development as well as hematopoiesis and is the target of chromosomal rearrangement and missense mutations in hematological malignancies and solid tumors[39,40]. Hereditary mutations in ETV6 are associated with a predisposition to hematological cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[41,42,43,44,45].

Alterations and prevalence: ETV6 translocations are prevalent in hematological malignancies and have been observed with numerous fusion partners[46]. The most recurrent translocation is t(12;21)(p13;q22), which results in the ETV6::RUNX1 fusion and is observed in 20-25% of childhood acute lymphoblastic leukemia (ALL) and 2% of adult ALL[46,47]. The t(5;12)(q33;p13) translocation, which results in the ETV6::PDGFRB fusion, is recurrent in chronic myelomonocytic leukemia (CMML)[46,48]. Other ETV6 fusions, including ETV6::PDGFRA, ETV6::NTRK2, ETV6::NTRK3, and ETV6::ABL1, are reported in hematological malignancies and solid tumors[40,46,49]. ETV6 fusions involving a receptor tyrosine kinase (RTK) fusion partner retains the ETV6 PNT domains and the tyrosine kinase domain of the RTK, leading to constitutive kinase activation[46,49]. Mutations in ETV6 are primarily missense, nonsense, or frameshift and are observed in 5% of diffuse large B-cell lymphoma (DLBCL) and uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of colorectal adenocarcinoma and stomach adenocarcinoma, and 2% of bladder urothelial carcinoma and uterine carcinosarcoma[7,8,38,50]. ETV6 mutations occur in the PNT and ETS domain of ETV6 and may impair ETV6 oligomerization or DNA-binding, respectively[38]. Biallelic deletion of ETV6 is observed in 4% of DLBCL, 3% of prostate adenocarcinoma, and 2% of lung adenocarcinoma[7,8]. Alterations in ETV6, in addition to ETV6::RUNX1 fusion, are also observed in pediatric cancers[46,49]. ETV6 fusions occur in 12% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[46,49]. Somatic mutations in ETV6 are observed in 2% of B-lymphoblastic leukemia/lymphoma and less than 1% of leukemia (3 in 354 cases), embryonal tumors (1 in 332 cases), and bone cancer (1 in 327 cases)[46,49]. Biallelic deletion of ETV6 is observed in 11% of B-lymphoblastic leukemia/lymphoma and 4% of leukemia[46,49].

Potential relevance: ETV6::NTRK3 fusion is useful as an ancillary diagnostic marker in congenital/infantile fibrosarcoma and inflammatory myofibroblastic tumors[51,52]. Nonsense or frameshift mutations in ETV6 are independently associated with poor prognosis in MDS[53]. However, ETV6::RUNX1 fusions are associated with standard risk in adults and favorable outcomes in children with ALL[54,55,56]. ETV6 fusions that partner with RTKs demonstrate response to various tyrosine kinase inhibitors such as imatinib, nilotinib, and entrectinib[57]. Specifically, individual case reports of an ETV6::PDGFRA fusion chronic eosinophilic leukemia patient and an ETV6::PDGFRB fusion CMML patient treated with imatinib demonstrated complete cytogenetic response (CCyR) and complete hematological responses, respectively[58,59]. Additionally, an ETV6::ABL1 fusion Ph-negative CML patient treated with nilotinib demonstrated CCyR and major molecular response (MMR) at 22 months from diagnosis[60]. In another case report, an ETV6::NTRK3 fusion mammary analogue secretory carcinoma (MASC) patient demonstrated partial response to entrectinib with an 89% reduction in tumor burden[61].

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1,

Genes Assayed (continued)

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

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

ESR1 p.(D538G) c.1613A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
elacestrant	●	●	●	✖	✖

* 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

BRCA2 p.(T1346Sfs*5) c.4037_4038delCT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	◑	○	◑	● (II)
bevacizumab + olaparib	○	○	○	○	✖
abiraterone + niraparib	○	○	○	✖	✖
niraparib	○	○	✖	○	✖
rucaparib	○	○	✖	○	✖
talazoparib + enzalutamide	○	○	✖	✖	✖
bevacizumab + niraparib	✖	○	✖	✖	✖
olaparib + abiraterone acetate	✖	○	✖	✖	✖
talazoparib	✖	✖	✖	●	● (II)
camrelizumab, fluzoparib, chemotherapy	✖	✖	✖	✖	● (II)
niraparib, dostarlimab	✖	✖	✖	✖	● (II)
niraparib, hormone therapy	✖	✖	✖	✖	● (II)
olaparib + hormone therapy	✖	✖	✖	✖	● (II)
olaparib, durvalumab, chemotherapy	✖	✖	✖	✖	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
ZEN-3694, talazoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
AZD-9574	✖	✖	✖	✖	● (I/II)
IDB-476	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
ATX-559	✖	✖	✖	✖	● (I)
axatilimab, olaparib	✖	✖	✖	✖	● (I)
HS-10502	✖	✖	✖	✖	● (I)
niraparib, chemotherapy	✖	✖	✖	✖	● (I)
novobiocin	✖	✖	✖	✖	● (I)
olaparib, chemotherapy	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)

ATR p.(R2001*) c.6001C>T

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

BAP1 deletion

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

LATS1 p.(L85Afs*6) c.253_254delCT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
SW-682	✖	✖	✖	✖	● (I)

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Vander et al. TGF-β receptors: In and beyond TGF-β signaling. Cell Signal. 2018 Dec;52:112-120. PMID: 30184463
3. Shi et al. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell. 2003 Jun 13;113(6):685-700. PMID: 12809600
4. Heldin et al. Role of Smads in TGFβ signaling. Cell Tissue Res. 2012 Jan;347(1):21-36. PMID: 21643690
5. Sorrentino et al. The type I TGF-beta receptor engages TRAF6 to activate TAK1 in a receptor kinase-independent manner. Nat Cell Biol. 2008 Oct;10(10):1199-207. PMID: 18758450
6. Ioannou et al. Smad4 and epithelial-mesenchymal transition proteins in colorectal carcinoma: an immunohistochemical study. J Mol Histol. 2018 Jun;49(3):235-244. PMID: 29468299
7. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
8. 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
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
29. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf

References (continued)

30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
31. 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
32. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
33. https://www.senhwabio.com//en/news/20220125
34. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. Cell Death Differ. 2017 Sep;24(9):1488-1501. PMID: 28644436
35. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. Semin Cancer Biol. 2018 Feb;48:1-17. PMID: 28591657
36. Meng et al. Mechanisms of Hippo pathway regulation. Genes Dev. 2016 Jan 1;30(1):1-17. PMID: 26728553
37. Yu et al. Mutation analysis of large tumor suppressor genes LATS1 and LATS2 supports a tumor suppressor role in human cancer. Protein Cell. 2015 Jan;6(1):6-11. PMID: 25482410
38. Wang et al. ETV6 mutation in a cohort of 970 patients with hematologic malignancies. Haematologica. 2014 Oct;99(10):e176-8. PMID: 24997145
39. Wang et al. The TEL/ETV6 gene is required specifically for hematopoiesis in the bone marrow. Genes Dev. 1998 Aug 1;12(15):2392-402. PMID: 9694803
40. Huret et al. Atlas of genetics and cytogenetics in oncology and haematology in 2013. Nucleic Acids Res. 2013 Jan;41(Database issue):D920-4. PMID: 23161685
41. Feurstein et al. Germline ETV6 mutations and predisposition to hematological malignancies. Int. J. Hematol. 2017 Aug;106(2):189-195. PMID: 28555414
42. Melazzini et al. Clinical and pathogenic features of ETV6-related thrombocytopenia with predisposition to acute lymphoblastic leukemia. Haematologica. 2016 Nov;101(11):1333-1342. PMID: 27365488
43. Zhang et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet. 2015 Feb;47(2):180-5. PMID: 25581430
44. Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. PMID: 35732831
45. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
46. De et al. ETV6 fusion genes in hematological malignancies: a review. Leuk. Res. 2012 Aug;36(8):945-61. PMID: 22578774
47. Pui et al. Acute lymphoblastic leukemia. N. Engl. J. Med. 2004 Apr 8;350(15):1535-48. PMID: 15071128
48. Golub et al. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell. 1994 Apr 22;77(2):307-16. PMID: 8168137
49. Taylor et al. Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. J. Clin. Invest. 2018 Aug 31;128(9):3819-3825. PMID: 29920189
50. Bejar et al. Clinical effect of point mutations in myelodysplastic syndromes. N. Engl. J. Med. 2011 Jun 30;364(26):2496-506. PMID: 21714648
51. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
52. Yamamoto et al. ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours. Histopathology. 2016 Jul;69(1):72-83. PMID: 26647767
53. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
54. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
55. NCCN Guidelines® - NCCN-Pediatric Acute Lymphoblastic Leukemia [Version 1.2026]
56. Mattano et al. Favorable Trisomies and ETV6-RUNX1 Predict Cure in Low-Risk B-Cell Acute Lymphoblastic Leukemia: Results From Children's Oncology Group Trial AALL0331. J Clin Oncol. 2021 May 10;39(14):1540-1552. PMID: 33739852
57. Mueller et al. t(4;12)(q12;p13) ETV6-rearranged AML without eosinophilia does not involve PDGFRA: relevance for imatinib insensitivity. Blood Adv. 2022 Jan 8;6(3):818-827. PMID: 34587239
58. Curtis et al. Two novel imatinib-responsive PDGFRA fusion genes in chronic eosinophilic leukaemia. Br. J. Haematol. 2007 Jul;138(1):77-81. PMID: 17555450
59. Curtis et al. A novel ETV6-PDGFRB fusion transcript missed by standard screening in a patient with an imatinib responsive chronic myeloproliferative disease. Leukemia. 2007 Aug;21(8):1839-41. Epub 2007 May 17. PMID: 17508004

References (continued)

60. Gancheva et al. Myeloproliferative neoplasm with ETV6-ABL1 fusion: a case report and literature review. Mol Cytogenet. 2013 Sep 20;6(1):39. doi: 10.1186/1755-8166-6-39. PMID: 24053143
61. Drilon et al. What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). Ann Oncol. 2016 May;27(5):920-6. doi: 10.1093/annonc/mdw042. Epub 2016 Feb 15. PMID: 26884591
62. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. Front Cell Neurosci. 2014;8:349. PMID: 25389387
63. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene. 2006 Mar 13;25(11):1659-72. PMID: 16550166
64. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. Br J Cancer. 2020 Apr;122(9):1277-1287. PMID: 32047295
65. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. Mol Carcinog. 2014 Apr;53(4):314-24. PMID: 23143693
66. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. Oncotarget. 2017 Jan 10;8(2):3640-3648. PMID: 27690298
67. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. PLoS One. 2015;10(5):e0127524. PMID: 26010150
68. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573
69. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
70. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
71. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
72. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
73. 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
74. 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
75. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
76. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
77. 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
78. Bonadona et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun 8;305(22):2304-10. PMID: 21642682
79. Engel et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106
80. Grant et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 Mar;148(3):556-64. PMID: 25479140
81. Hu et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018 Jun 19;319(23):2401-2409. PMID: 29922827
82. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
83. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
84. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
85. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430
86. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
87. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087

References (continued)

88. 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
89. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
90. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
91. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
92. 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
93. Berends et al. MLH1 and MSH2 protein expression as a pre-screening marker in hereditary and non-hereditary endometrial hyperplasia and cancer. Int. J. Cancer. 2001 May 1;92(3):398-403. PMID: 11291077
94. Gausachs et al. MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: a cost-effectiveness study. Eur. J. Hum. Genet. 2012 Jul;20(7):762-8. PMID: 22274583
95. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. Clin. Cancer Res. 2013 May 1;19(9):2301-9. PMID: 23406774
96. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3). PMID: 32046099
97. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 2014 Jan;171(1):24-37. PMID: 24117156
98. Ahn et al. Map2k4 functions as a tumor suppressor in lung adenocarcinoma and inhibits tumor cell invasion by decreasing peroxisome proliferator-activated receptor γ2 expression. Mol. Cell. Biol. 2011 Nov;31(21):4270-85. PMID: 21896780
99. Robinson et al. Mitogen-activated protein kinase kinase 4/c-Jun NH2-terminal kinase kinase 1 protein expression is subject to translational regulation in prostate cancer cell lines. Mol. Cancer Res. 2008 Mar;6(3):501-8. PMID: 18337456
100. Xue et al. MAP3K1 and MAP2K4 mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. Cell Res. 2018 Jul;28(7):719-729. PMID: 29795445
101. Wenzel et al. Loss of the nuclear Wnt pathway effector TCF7L2 promotes migration and invasion of human colorectal cancer cells. Oncogene. 2020 May;39(19):3893-3909. PMID: 32203164
102. Hong et al. MAD2B, a novel TCF4-binding protein, modulates TCF4-mediated epithelial-mesenchymal transdifferentiation. J Biol Chem. 2009 Jul 17;284(29):19613-22. PMID: 19443654
103. He et al. Identification of c-MYC as a target of the APC pathway. Science. 1998 Sep 4;281(5382):1509-12. PMID: 9727977
104. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell. Physiol. Biochem. 2018;51(6):2647-2693. PMID: 30562755
105. Stamos et al. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a007898. PMID: 23169527
106. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. Mol Cancer. 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
107. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J. Cell. Sci. 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
108. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum. Mol. Genet. 1992 Jul;1(4):229-33. PMID: 1338904
109. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
110. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc. Natl. Acad. Sci. U.S.A. 2000 Mar 28;97(7):3352-7. PMID: 10737795
111. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. Nucleic Acids Res. 1998 Jan 1;26(1):269-70. PMID: 9399850
112. Martins et al. Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. Nat Immunol. 2006 May;7(5):457-65. PMID: 16565721
113. Nutt et al. BLIMP1 guides the fate of effector B and T cells. Nat Rev Immunol. 2007 Dec;7(12):923-7. PMID: 17965637
114. Fu et al. New insights into Blimp-1 in T lymphocytes: a divergent regulator of cell destiny and effector function. J Biomed Sci. 2017 Jul 21;24(1):49. PMID: 28732506

References (continued)

115. Kallies et al. Terminal differentiation of lymphocytes depends on Blimp-1. Curr Opin Immunol. 2007 Apr;19(2):156-62. PMID: 17291741
116. Amé et al. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93. PMID: 15273990
117. Morales et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr. 2014;24(1):15-28. PMID: 24579667
118. Prawira et al. Assessment of PARP4 as a candidate breast cancer susceptibility gene. Breast Cancer Res Treat. 2019 Aug;177(1):145-153. PMID: 31119570
119. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
120. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
121. Merchant et al. Suppressor of fused regulates Gli activity through a dual binding mechanism. Mol Cell Biol. 2004 Oct;24(19):8627-41. PMID: 15367681
122. Zhang et al. Structural insight into the mutual recognition and regulation between Suppressor of Fused and Gli/Ci. Nat Commun. 2013;4:2608. PMID: 24217340
123. Cherry et al. Structural basis of SUFU-GLI interaction in human Hedgehog signalling regulation. Acta Crystallogr D Biol Crystallogr. 2013 Dec;69(Pt 12):2563-79. PMID: 24311597
124. Doheny et al. Hedgehog Signaling and Truncated GLI1 in Cancer. Cells. 2020 Sep 17;9(9). PMID: 32957513
125. Guerrini-Rousseau et al. Germline SUFU mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis. Neuro Oncol. 2018 Jul 5;20(8):1122-1132. PMID: 29186568
126. D'Alessandro et al. BRCA2 controls DNA:RNA hybrid level at DSBs by mediating RNase H2 recruitment. Nat Commun. 2018 Dec 18;9(1):5376. PMID: 30560944
127. Aden et al. Epithelial RNase H2 Maintains Genome Integrity and Prevents Intestinal Tumorigenesis in Mice. Gastroenterology. 2019 Jan;156(1):145-159.e19. PMID: 30273559
128. Maréchal et al. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol. 2013 Sep 1;5(9). PMID: 24003211
129. 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
130. Flynn et al. ATR: a master conductor of cellular responses to DNA replication stress. Trends Biochem. Sci. 2011 Mar;36(3):133-40. PMID: 20947357
131. Tibbetts et al. Functional interactions between BRCA1 and the checkpoint kinase ATR during genotoxic stress. Genes Dev. 2000 Dec 1;14(23):2989-3002. PMID: 11114888
132. Bao et al. ATR/ATM-mediated phosphorylation of human Rad17 is required for genotoxic stress responses. Nature. 2001 Jun 21;411(6840):969-74. PMID: 11418864
133. Tanaka et al. Germline mutation in ATR in autosomal- dominant oropharyngeal cancer syndrome. Am. J. Hum. Genet. 2012 Mar 9;90(3):511-7. PMID: 22341969
134. Durocher et al. Mutation analysis and characterization of ATR sequence variants in breast cancer cases from high-risk French Canadian breast/ovarian cancer families. BMC Cancer.2006 Sep 29;6:230. PMID: 17010193
135. Katsumura et al. The GATA factor revolution in hematology. Blood. 2017 Apr 13;129(15):2092-2102. PMID: 28179282
136. Orkin. GATA-binding transcription factors in hematopoietic cells. Blood. 1992 Aug 1;80(3):575-81. PMID: 1638017
137. Takaku et al. GATA3 in Breast Cancer: Tumor Suppressor or Oncogene?. Gene Expr. 2015;16(4):163-8. PMID: 26637396
138. Chou et al. GATA3 in development and cancer differentiation: cells GATA have it!. J Cell Physiol. 2010 Jan;222(1):42-9. PMID: 19798694
139. Mehra et al. Identification of GATA3 as a breast cancer prognostic marker by global gene expression meta-analysis. Cancer Res. 2005 Dec 15;65(24):11259-64. PMID: 16357129
140. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014 Sep;13(9):673-91. PMID: 25131830
141. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. Biomed Pharmacother. 2016 Dec;84:284-290. PMID: 27665474
142. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. Cold Spring Harb Perspect Med. 2016 Oct 3;6(10). PMID: 27599530
143. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf

References (continued)

144. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
145. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
146. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf
147. Yang et al. Mitogen-activated protein kinase kinase kinase 4 deficiency in intrahepatic cholangiocarcinoma leads to invasive growth and epithelial-mesenchymal transition. Hepatology. 2015 Dec;62(6):1804-16. PMID: 26340507
148. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. Nat Commun. 2021 Apr 6;12(1):2047. PMID: 33824349
149. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. Am. J. Respir. Cell Mol. Biol. 2018 Aug;59(2):200-214. PMID: 29420051
150. Roussel. The INK4 family of cell cycle inhibitors in cancer. Oncogene. 1999 Sep 20;18(38):5311-7. PMID: 10498883
151. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). Biochem. Biophys. Res. Commun. 1999 Aug 27;262(2):534-8. PMID: 10462509
152. Hill et al. The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet. 2013;14:257-79. PMID: 23875803
153. Kim et al. The regulation of INK4/ARF in cancer and aging. Cell. 2006 Oct 20;127(2):265-75. PMID: 17055429
154. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. Mayo Clin. Proc. 2008 Jul;83(7):825-46. PMID: 18613999
155. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. J. Invest. Dermatol. 2007 May;127(5):1234-43. PMID: 17218939
156. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. Ann. Surg. 2002 Dec;236(6):730-7. PMID: 12454511
157. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. Clin Cancer Res. 2021 Jul 15;27(14):4025-4035. PMID: 34074656
158. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2025]
159. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2025]
160. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020 Jul;30(4):844-856. PMID: 32307792
161. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. J Transl Med. 2019 Jul 29;17(1):245. PMID: 31358010
162. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res. 2013 Aug;33(8):2997-3004. PMID: 23898052
163. von et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmocological Inhibitors of the CDK4/6 Cell-Cycle Pathway. Cancer Res. 2015 Sep 15;75(18):3823-31. PMID: 26183925
164. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-oncology. 2012 Jul;14(7):870-81. PMID: 22711607
165. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. Oncotarget. 2018 Sep 7;9(70):33247-33248. PMID: 30279955
166. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J. Clin. Oncol. 2014 Dec 10;32(35):3930-8. PMID: 25267748
167. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. J. Natl. Cancer Inst. 2018 Dec 1;110(12):1393-1399. PMID: 29878161
168. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. Cancer Clin Oncol. 2013;2(1):51-61. PMID: 23935769
169. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. Cancer Discov. 2013 Jan;3(1):35-43. PMID: 23208470
170. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
171. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751
172. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
173. McKinney et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. Cancer Discov. 2017 Apr;7(4):369-379. PMID: 28122867
174. Murali et al. Tumours associated with BAP1 mutations. Pathology. 2013 Feb;45(2):116-26. PMID: 23277170

References (continued)

175. Wiesner et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat. Genet. 2011 Aug 28;43(10):1018-21. PMID: 21874003
176. Wadt et al. A cryptic BAP1 splice mutation in a family with uveal and cutaneous melanoma, and paraganglioma. Pigment Cell Melanoma Res. 2012 Nov;25(6):815-8. PMID: 22889334
177. Cheung et al. Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma. Cancer Genet. 2013 May;206(5):206-10. PMID: 23849051
178. Njauw et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. PLoS ONE. 2012;7(4):e35295. PMID: 22545102
179. Pilarski et al. Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases. Genes Chromosomes Cancer. 2014 Feb;53(2):177-82. PMID: 24243779
180. Popova et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am. J. Hum. Genet. 2013 Jun 6;92(6):974-80. PMID: 23684012
181. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. J Clin Med. 2017 Jan 5;6(1). PMID: 28067794
182. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 2018;14(2):111-123. PMID: 29483830
183. Cicenas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. Cancers (Basel). 2017 Apr 28;9(5). PMID: 28452926
184. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. Biochem. Biophys. Res. Commun. 2003 Jul 11;306(4):799-804. PMID: 12821112
185. Mehrvarz et al. Association of SMAD4 mutation with patient demographics, tumor characteristics, and clinical outcomes in colorectal cancer. PLoS ONE. 2017;12(3):e0173345. PMID: 28267766
186. Yan et al. Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer. Clin. Cancer Res. 2016 Jun 15;22(12):3037-47. PMID: 26861460
187. Voorneveld et al. A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer. Transl Oncol. 2015 Feb;8(1):18-24. PMID: 25749173
188. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. Transl Oncol. 2016 Feb;9(1):1-7. PMID: 26947875
189. Boulay et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. Br. J. Cancer. 2002 Sep 9;87(6):630-4. PMID: 12237773
190. Kozak et al. Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer. J. Clin. Pathol. 2015 May;68(5):341-5. PMID: 25681512
191. Ozawa et al. SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells. Clin. Cancer Res. 2017 Sep 1;23(17):5162-5175. PMID: 28522603
192. Paterni et al. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014 Nov;90:13-29. PMID: 24971815
193. Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen receptors. Pharmacol. Rev. 2006 Dec;58(4):773-81. PMID: 17132854
194. Marino et al. Estrogen signaling multiple pathways to impact gene transcription. Curr. Genomics. 2006;7(8):497-508. PMID: 18369406
195. Chang. Tamoxifen resistance in breast cancer. Biomol Ther (Seoul). 2012 May;20(3):256-67. PMID: 24130921
196. Toy et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat. Genet. 2013 Dec;45(12):1439-45. PMID: 24185512
197. Jeselsohn et al. Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor-Positive Breast Cancer. Clin. Cancer Res. 2014 Apr 1;20(7):1757-1767. PMID: 24398047
198. Robinson et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet. 2013 Dec;45(12):1446-51. doi: 10.1038/ng.2823. Epub 2013 Nov 3. PMID: 24185510
199. Hartmaier et al. Recurrent hyperactive ESR1 fusion proteins in endocrine therapy-resistant breast cancer. Ann. Oncol. 2018 Apr 1;29(4):872-880. PMID: 29360925
200. Matissek et al. Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor-Positive Breast Cancer. Cancer Discov. 2018 Mar;8(3):336-353. PMID: 29242214
201. Lei et al. ESR1 fusions drive endocrine therapy resistance and metastasis in breast cancer. Mol Cell Oncol. 2018;5(6):e1526005. PMID: 30525098

References (continued)

202. Lei et al. Functional Annotation of ESR1 Gene Fusions in Estrogen Receptor-Positive Breast Cancer. Cell Rep. 2018 Aug 7;24(6):1434-1444.e7. PMID: 30089255
203. Basudan et al. Frequent ESR1 and CDK Pathway Copy-Number Alterations in Metastatic Breast Cancer. Mol. Cancer Res. 2019 Feb;17(2):457-468. PMID: 30355675
204. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639Orig1s001lbl.pdf
205. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2025]
206. https://www.accutarbio.com/accutar-biotechnology-receives-fda-fast-track-designation-for-ac699-in-er-her2-breast-cancer/
207. https://sermonixpharma.com/sermonix-receives-fda-fast-track-designation-for-investigational-drug-lasofoxifene/
208. https://www.astrazeneca.com/content/dam/az/PDF/2022/h1-2022/H1-2022-results-announcement.pdf
209. https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA
210. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/17970s37s44s49lbl.pdf
211. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021344s044lbl.pdf
212. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020726s043lbl.pdf
213. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020753s025lbl.pdf
214. Tamoxifen--an update on current data and where it can now be used. Breast Cancer Res. Treat. 2002 Oct;75 Suppl 1:S7-12; discussion S33-5. PMID: 12353826
215. Kim et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. J. Clin. Oncol. 2011 Nov 1;29(31):4160-7. PMID: 21947828
216. Jeselsohn et al. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015 Oct;12(10):573-83. PMID: 26122181
217. Angus et al. ESR1 mutations: Moving towards guiding treatment decision-making in metastatic breast cancer patients. Cancer Treat. Rev. 2017 Jan;52:33-40. PMID: 27886589
218. Reinert et al. Clinical Implications of ESR1 Mutations in Hormone Receptor-Positive Advanced Breast Cancer. . Front Oncol. 2017 Mar 15;7:26. PMID: 28361033
219. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011 Mar;75(1):50-83. PMID: 21372320
220. Roskoski. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol. Res. 2012 Aug;66(2):105-43. PMID: 22569528
221. Roskoski. MEK1/2 dual-specificity protein kinases: structure and regulation. Biochem. Biophys. Res. Commun. 2012 Jan 6;417(1):5-10. PMID: 22177953
222. Marampon et al. Biological Rationale for Targeting MEK/ERK Pathways in Anti-Cancer Therapy and to Potentiate Tumour Responses to Radiation. Int J Mol Sci. 2019 May 23;20(10). PMID: 31126017