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

Patient Name: 김광철
Gender: M
Sample ID: N25-116

Primary Tumor Site: prostate
Collection Date: 2024.07.10

Sample Cancer Type: Prostate Cancer

Table of Contents	Page

Report Highlights

4 Relevant Biomarkers
3 Therapies Available
7 Clinical Trials

Relevant Prostate Cancer Findings

Gene	Finding
EGFR	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***3.83 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	3
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	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

*CUL4A deletion, FAT1 p.(T2369Cfs*2) c.7105_7106delACinsT, MSH3 p.(A68Sfs*20) c.191_200dup, Microsatellite stable, PARP4 deletion, PPP2R2A deletion, RNASEH2B deletion, RPA1 deletion, STK11 deletion, TCF7L2 deletion, MAP3K1 deletion, HLA-A p.(L180*) c.539T>A, TPP2 deletion, MGA p.(L1061*) c.3181delC, MGA p.(Y2518Lfs*20) c.7552_7553insT, NQO1 p.(P187S) c.559C>T, NCOR1 deletion, DSC1 deletion, SMAD2 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FAT1	p.(T2369Cfs*2)	c.7105_7106delACinsT	.	chr4:187540634	6.35%	NM_005245.4	frameshift Block Substitution
MSH3	p.(A68Sfs*20)	c.191_200dup	.	chr5:79950737	5.07%	NM_002439.5	frameshift Insertion
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	31.18%	NM_001242758.1	nonsense
MGA	p.(L1061*)	c.3181delC	.	chr15:42005444	27.84%	NM_001164273.1	nonsense
MGA	p.(Y2518Lfs*20)	c.7552_7553insT	.	chr15:42054365	33.99%	NM_001164273.1	frameshift Insertion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	45.20%	NM_000903.3	missense
MSH6	p.(Y1287C)	c.3860A>G	.	chr2:48033649	44.85%	NM_000179.3	missense
MAML3	p.(Q488_Q494delinsHDS)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACACGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	40.12%	NM_018717.5	nonframeshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	56.40%	NM_018717.5	frameshift Block Substitution
CBFB	p.(F153V)	c.457T>G	.	chr16:67116173	49.37%	NM_022845.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.61
PTEN	chr10:89623659	0	0.35
RB1	chr13:48877953	0.71	0.58
SMAD4	chr18:48573387	0.6	0.54
CUL4A	chr13:113863977	0.83	0.62
PARP4	chr13:25000551	0.57	0.53
PPP2R2A	chr8:26149298	0.08	0.38
RNASEH2B	chr13:51484145	0.77	0.6
RPA1	chr17:1733385	0.83	0.62
STK11	chr19:1206847	0.35	0.46
TCF7L2	chr10:114710485	0.72	0.59
MAP3K1	chr5:56111388	0.86	0.63

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
TPP2	chr13:103249399	0.85	0.63
NCOR1	chr17:15935586	0.97	0.66
DSC1	chr18:28710424	0.08	0.37
SMAD2	chr18:45368152	0.75	0.6
CTNND2	chr5:10988230	0.78	0.61
PRDM9	chr5:23509577	0.45	0.49
SETBP1	chr18:42281265	0.46	0.5

Biomarker Descriptions

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[81,82]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer[83] and in men for breast and prostate cancer[84,85]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer[86].테스트 입니다.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer[87,88,89,90,91,92,93]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[6,7].

Potential clinical 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)[94]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[95,96]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[] (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 who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib[] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib[] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status[97]. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[98]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[99].

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[25]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[26,27]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[28]. Germline mutations in PTEN are linked to

Biomarker Descriptions (continued)

hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[29]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[30].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[6,7]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[27,31,32,33,34]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[6,7].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[35,36]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[38] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[67,68]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[69]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[67,68,70]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[71].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[7]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[7]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[72,73,74].

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

SMAD4 deletion

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[104,105]. 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[105,106,107]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[104,105]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[104]. 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[7,107,108]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[6,7,109].

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[105,107,110,111,112]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[113,114]. 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)[114]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[115].

Biomarker Descriptions (continued)

CUL4A deletion

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[12,13]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[14]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[14,15]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[13]. CUL4A is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[15]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[14,15].

Alterations and prevalence: Somatic mutations in CUL4A are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma[6,7]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[6,7]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[6,7]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[6,7].

Potential relevance: Currently, no therapies are approved for CUL4A aberrations.

FAT1 p.(T2369Cfs*2) c.7105_7106delACinsT

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[12,57]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[57]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[57]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[57]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[57].

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

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

MSH3 p.(A68Sfs*20) c.191_200dup

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[12]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[58,59]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[58,59]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[60].

Alterations and prevalence: Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma[6,7]. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma[6,7].

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[120]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[121,122]. MSI is closely tied to the status of the mismatch repair (MMR)

Biomarker Descriptions (continued)

genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[123]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[124]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[124]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[125,126,127,128,129]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[122]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[121,122,126,130].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[121,122,131,132]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[131,132].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[133] (2014) and nivolumab[134] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[133] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[133]. Dostarlimab[135] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[127,136]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[137] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[127,138,139]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[139]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[140,141]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[140,141].

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[12]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[16]. 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, nucleic acid metabolism, and regulation of chromatin structure[16,17]. PARP enzymes are involved in several DNA repair pathways[16,17]. 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[18].

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[6,7]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[6,7].

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[19,20]. 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[21] (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[21] 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[22] (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[23] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[24] (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.

Biomarker Descriptions (continued)

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[44,45]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[46]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[44].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[44,45,47,48]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[6].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[44]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[49].

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[12]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[50,51]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[50]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[50].

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

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

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[12]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[61]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[61]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[61].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[6,7]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and

Biomarker Descriptions (continued)

tumor suppression[1]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[2,3].

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer[4,5,6,7]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[6,7]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[2,5,6,7,8].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260[9] in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[10]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[11].

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[12,142]. 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[142,143,144]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[142]. 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[142].

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[6,7]. 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[6,7].

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

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[12]. Activation of MAPK proteins occurs through a kinase signaling cascade[62,63,64]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[62,63,64]. 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[62,63,64]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[65]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[65]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[65].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[6,7]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[65]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[6,7].

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

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[12]. 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[75]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[76]. 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

Biomarker Descriptions (continued)

amino acids, to the immune system to distinguish self from non-self[77,78,79]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[80].

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[6,7]. Biallelic loss of HLA-A is observed in 4% of DLBCL[6,7].

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

TPP2 deletion

tripeptidyl peptidase 2

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[12]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[66]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[66]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[66].

Alterations and prevalence: Somatic mutations in TPP2 are observed in 8% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 4% of bladder urothelial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL), kidney renal papillary cell carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[6,7]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[6,7].

Potential relevance: Currently, no therapies are approved for TPP2 aberrations.

MGA p.(L1061*) c.3181delC, MGA p.(Y2518Lfs*20) c.7552_7553insT

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[12,100]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[101]. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation[100]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[102]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[103].

Alterations and prevalence: Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma[6,7]. MGA biallelic deletion is observed in 6% of diffuse large B-cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy[103].

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[12,52,53]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[52,53,54,55]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[53]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[53,56].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[6,7]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell

Biomarker Descriptions (continued)

lymphoma, and bladder urothelial carcinoma[6,7]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[6,7].

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

DSC1 deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3[12]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[39]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[40]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis[39,41,42,43].

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma[6,7]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

SMAD2 deletion

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes[12,104,105]. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[104,105]. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF-β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development[105]. Following activation of type I TGF-β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes[116,117]. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2[117,118].

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma[6,7]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[6,7,117]. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex[6,7,119]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for SMAD2 aberrations.

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

BRCA2 deletion

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

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bortezomib	✖	✖	✖	✖	● (II)
hormone therapy, hormone therapy + chemotherapy	✖	✖	✖	✖	● (II)
palbociclib, gedatolisib	✖	✖	✖	✖	● (I)

RB1 deletion

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

SMAD4 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***15.06%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(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 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. Li et al. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (Review). Oncol. Rep. 2015 Dec;34(6):2821-6. PMID: 26398719
2. Zhou et al. LKB1 Tumor Suppressor: Therapeutic Opportunities Knock when LKB1 Is Inactivated. Genes Dis. 2014 Sep 1;1(1):64-74. PMID: 25679014
3. Hemminki et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature. 1998 Jan 8;391(6663):184-7. PMID: 9428765
4. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
7. 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
8. Sanchez-Cespedes et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. Cancer Res. 2002 Jul 1;62(13):3659-62. PMID: 12097271
9. https://ir.tangotx.com//news-releases/news-release-details/tango-therapeutics-announces-first-patient-dosed-tng260-phase-12
10. Koyama et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. Cancer Res. 2016 Mar 1;76(5):999-1008. PMID: 26833127
11. Skoulidis et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov. 2018 Jul;8(7):822-835. PMID: 29773717
12. 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
13. Sarikas et al. The cullin protein family. Genome Biol. 2011;12(4):220. PMID: 21554755
14. Sang et al. The role and mechanism of CRL4 E3 ubiquitin ligase in cancer and its potential therapy implications. Oncotarget. 2015 Dec 15;6(40):42590-602. PMID: 26460955
15. Cheng et al. The emerging role for Cullin 4 family of E3 ligases in tumorigenesis. Biochim Biophys Acta Rev Cancer. 2019 Jan;1871(1):138-159. PMID: 30602127
16. Amé et al. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93. PMID: 15273990
17. 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
18. 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
19. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
20. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
25. Milella et al. PTEN: Multiple Functions in Human Malignant Tumors. Front Oncol. 2015 Feb 16;5:24. doi: 10.3389/fonc.2015.00024. eCollection 2015. PMID: 25763354
26. Song et al. The functions and regulation of the PTEN tumour suppressor. Nat. Rev. Mol. Cell Biol. 2012 Apr 4;13(5):283-96. PMID: 22473468
27. Chalhoub et al. PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol. 2009;4:127-50. PMID: 18767981
28. Mansour et al. Loss of PTEN-assisted G2/M checkpoint impedes homologous recombination repair and enhances radio-curability and PARP inhibitor treatment response in prostate cancer. Sci Rep. 2018 Mar 2;8(1):3947. PMID: 29500400
29. Leslie et al. Inherited PTEN mutations and the prediction of phenotype. Semin. Cell Dev. Biol. 2016 Apr;52:30-8. PMID: 26827793
30. Tan et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin. Cancer Res. 2012 Jan 15;18(2):400-7. PMID: 22252256

References (continued)

31. Dillon et al. Therapeutic targeting of cancers with loss of PTEN function. Curr Drug Targets. 2014 Jan;15(1):65-79. PMID: 24387334
32. Papa et al. Cancer-associated PTEN mutants act in a dominant-negative manner to suppress PTEN protein function. Cell. 2014 Apr 24;157(3):595-610. PMID: 24766807
33. Kato et al. Functional evaluation of p53 and PTEN gene mutations in gliomas. Clin. Cancer Res. 2000 Oct;6(10):3937-43. PMID: 11051241
34. Han et al. Functional evaluation of PTEN missense mutations using in vitro phosphoinositide phosphatase assay. Cancer Res. 2000 Jun 15;60(12):3147-51. PMID: 10866302
35. Mendes-Pereira et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med. 2009 Sep;1(6-7):315-22. PMID: 20049735
36. Bian et al. PTEN deficiency sensitizes endometrioid endometrial cancer to compound PARP-PI3K inhibition but not PARP inhibition as monotherapy. Oncogene. 2018 Jan 18;37(3):341-351. PMID: 28945226
37. https://www.senhwabio.com//en/news/20220125
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf
39. Chidgey et al. Desmosomes: a role in cancer?. Br J Cancer. 2007 Jun 18;96(12):1783-7. PMID: 17519903
40. Dubash et al. Desmosomes. Curr Biol. 2011 Jul 26;21(14):R529-31. PMID: 21783027
41. Hardman et al. Desmosomal cadherin misexpression alters beta-catenin stability and epidermal differentiation. Mol Cell Biol. 2005 Feb;25(3):969-78. PMID: 15657425
42. Wang et al. Lower DSC1 expression is related to the poor differentiation and prognosis of head and neck squamous cell carcinoma (HNSCC). J Cancer Res Clin Oncol. 2016 Dec;142(12):2461-2468. PMID: 27601166
43. Oshiro et al. Epigenetic silencing of DSC3 is a common event in human breast cancer. Breast Cancer Res. 2005;7(5):R669-80. PMID: 16168112
44. Kalev et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. Cancer Res. 2012 Dec 15;72(24):6414-24. PMID: 23087057
45. Álvarez-Fernández et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. Cell Death Differ. 2018 May;25(5):828-840. PMID: 29229993
46. Perrotti et al. Protein phosphatase 2A: a target for anticancer therapy. Lancet Oncol. 2013 May;14(6):e229-38. PMID: 23639323
47. Beca et al. Altered PPP2R2A and Cyclin D1 Expression Defines a Subgroup of Aggressive Luminal-Like Breast Cancer. BMC Cancer. 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. PMID: 25879784
48. Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52. PMID: 22522925
49. NCCN Guidelines® - NCCN-Prostate Cancer [Version 2.2025]
50. 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
51. 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
52. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. Front Immunol. 2020;11:569358. PMID: 33117357
53. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. Pharmacol Res. 2016 Jun;108:75-79. PMID: 27149915
54. Bhaskara et al. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell. 2010 Nov 16;18(5):436-47. PMID: 21075309
55. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. Genes Dev. 2013 Apr 15;27(8):819-35. PMID: 23630073
56. Noblejas-López et al. Evaluation of transcriptionally regulated genes identifies NCOR1 in hormone receptor negative breast tumors and lung adenocarcinomas as a potential tumor suppressor gene. PLoS One. 2018;13(11):e0207776. PMID: 30485330
57. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
58. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
59. Tamura et al. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. Int J Clin Oncol. 2019 Sep;24(9):999-1011. PMID: 31273487

References (continued)

60. Ikeda et al. Close correlation between mutations of E2F4 and hMSH3 genes in colorectal cancers with microsatellite instability. Cancer Res. 1998 Feb 15;58(4):594-8. PMID: 9485005
61. Binz et al. Replication Protein A phosphorylation and the cellular response to DNA damage. DNA Repair, 01 Aug 2004, 3(8-9):1015-1024. PMID: 15279788
62. 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
63. 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
64. 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
65. Pham et al. MAP3K1: Genomic Alterations in Cancer and Function in Promoting Cell Survival or Apoptosis. Genes Cancer. 2013 Nov;4(11-12):419-26. PMID: 24386504
66. Wiemhoefer et al. Tripeptidyl Peptidase II Mediates Levels of Nuclear Phosphorylated ERK1 and ERK2. Mol Cell Proteomics. 2015 Aug;14(8):2177-93. PMID: 26041847
67. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev . 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
68. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. J. Clin. Invest. 2012 Feb;122(2):425-34. PMID: 22293180
69. Dyson. RB1: a prototype tumor suppressor and an enigma. Genes Dev. 2016 Jul 1;30(13):1492-502. PMID: 27401552
70. Cobrinik. Pocket proteins and cell cycle control. Oncogene. 2005 Apr 18;24(17):2796-809. PMID: 15838516
71. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam. Cancer. 2012 Jun;11(2):225-33. PMID: 22205104
72. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. . Oman J Ophthalmol . May-Aug 2016;9(2):116-8. PMID: 27433042
73. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. Leukemia. 1999 Sep;13(9):1367-73. PMID: 10482987
74. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. Ophthalmology. 2007 Jul;114(7):1378-83. PMID: 17613328
75. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
76. 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
77. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
78. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
79. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
80. 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
81. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553
82. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514
83. 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
84. 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
85. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
86. NCCN Guidelines® - NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian [Version 1.2018]. NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian

References (continued)

87. ARUP Laboratories University of Utah Department of Pathology.. https://arupconsult.com/ati/hereditary-breast-and-ovarian-cancer
88. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
89. 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
90. 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
91. 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
92. 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
93. 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
94. 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
95. 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
96. 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
97. Ison et al. FDA Approval Summary: Niraparib for the Maintenance Treatment of Patients with Recurrent Ovarian Cancer in Response to Platinum-Based Chemotherapy. Clin. Cancer Res. 2018 Sep 1;24(17):4066-4071. PMID: 29650751
98. 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
99. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
100. Hurlin et al. The MAX-interacting transcription factor network. Semin. Cancer Biol. 2006 Aug;16(4):265-74. PMID: 16908182
101. Susan. An Overview of the Basic Helix-Loop-Helix Proteins. Genome Biol. 2004;5(6):226. PMID: 15186484
102. Llabata et al. Multi-Omics Analysis Identifies MGA as a Negative Regulator of the MYC Pathway in Lung Adenocarcinoma. Mol Cancer Res. 2020 Apr;18(4):574-584. PMID: 31862696
103. Sun et al. MGA Mutation as a Novel Biomarker for Immune Checkpoint Therapies in Non-Squamous Non-Small Cell Lung Cancer. Front Pharmacol. 2021;12:625593. PMID: 33927616
104. 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
105. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 2018;14(2):111-123. PMID: 29483830
106. Cicenas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. Cancers (Basel). 2017 Apr 28;9(5). PMID: 28452926
107. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. Biochem. Biophys. Res. Commun. 2003 Jul 11;306(4):799-804. PMID: 12821112
108. 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
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. 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
111. 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
112. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. Transl Oncol. 2016 Feb;9(1):1-7. PMID: 26947875
113. 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
114. 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

References (continued)

115. 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
116. Massagué et al. Smad transcription factors. Genes Dev. 2005 Dec 1;19(23):2783-810. PMID: 16322555
117. Fleming et al. SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. Cancer Res. 2013 Jan 15;73(2):725-35. PMID: 23139211
118. Fukuchi et al. Lack of activated Smad2 in transforming growth factor-beta signaling is an unfavorable prognostic factor in patients with esophageal squamous cell carcinoma. J Surg Oncol. 2006 Jul 1;94(1):51-6. PMID: 16788944
119. Galka-Marciniak et al. A pan-cancer atlas of somatic mutations in miRNA biogenesis genes. Nucleic Acids Res. 2021 Jan 25;49(2):601-620. PMID: 33406242
120. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
121. 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
122. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
123. 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
124. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57. PMID: 9823339
125. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. Cancer Res. 2002 Jan 1;62(1):53-7. PMID: 11782358
126. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
127. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
128. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
129. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. Medicine (Baltimore). 2015 Dec;94(50):e2260. PMID: 26683947
130. 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
131. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. Nat Commun. 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
132. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
133. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
134. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
135. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
136. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
137. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
138. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N. Engl. J. Med. 2003 Jul 17;349(3):247-57. PMID: 12867608
139. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann. Oncol. 2015 Jan;26(1):126-32. PMID: 25361982
140. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
141. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
142. 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
143. 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
144. He et al. Identification of c-MYC as a target of the APC pathway. Science. 1998 Sep 4;281(5382):1509-12. PMID: 9727977