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Patient Name: 고재희
Gender: F
Sample ID: N25-146

Primary Tumor Site: Endometrium
Collection Date: 2025.07.24

Sample Cancer Type: Endometrial Endometrioid Adenocarcinoma

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Report Highlights

3 Relevant Biomarkers
14 Therapies Available
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Relevant Endometrial Endometrioid Adenocarcinoma Findings

Gene	Finding
BRAF	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Microsatellite Status	***Microsatellite instability-High***
Tumor Mutational Burden	***19.06 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Microsatellite instability-High*	**dostarlimab** [2 / I, II+] **pembrolizumab** [1, 2 / I, II+] **dostarlimab + chemotherapy** [2] avelumab [II+] nivolumab [II+]	**ipilimumab + nivolumab** [1, 2 / I, II+] **nivolumab** [1 / I, II+] **pembrolizumab** [1, 2 / I, II+] cemiplimab [I, II+] dostarlimab [I, II+] retifanlimab [I, II+] tislelizumab [I, II+] toripalimab [I, II+] nivolumab + chemotherapy [I] pembrolizumab + chemotherapy [I] avelumab [II+] durvalumab + tremelimumab [II+]	39

*** 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	*ESR1 p.(L536H) c.1607T>A* estrogen receptor 1 Allele Frequency: 19.31% Locus: chr6:152419920 Transcript: NM_001122740.2	None*	**elacestrant** [1, 2 / I, II+]	0
IIC	*ARID1A p.(Q1835*) c.5503C>T* AT-rich interaction domain 1A Allele Frequency: 20.04% Locus: chr1:27105892 Transcript: NM_006015.6	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

*KMT2D p.(L2331Pfs*46) c.6991_6992insC, PIK3R1 p.(T576del) c.1727_1729delCGA, PTEN p.(K267Rfs*9) c.800delA, PTEN p.(P339Rfs*2) c.1014_1023delTCCAAATTTT, SOS1 p.(N233Y) c.697A>T, HLA-B deletion, CTCF p.(G318Qfs*16) c.950_951dup, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ESR1	p.(L536H)	c.1607T>A	COSM6843697	chr6:152419920	19.31%	NM_001122740.2	missense
ARID1A	p.(Q1835*)	c.5503C>T	.	chr1:27105892	20.04%	NM_006015.6	nonsense
KMT2D	p.(L2331Pfs*46)	c.6991_6992insC	.	chr12:49434561	6.70%	NM_003482.4	frameshift Insertion
PIK3R1	p.(T576del)	c.1727_1729delCGA	COSM35737	chr5:67591131	18.41%	NM_181523.3	nonframeshift Deletion
PTEN	p.(K267Rfs*9)	c.800delA	COSM5809	chr10:89717769	19.34%	NM_000314.8	frameshift Deletion
PTEN	p.(P339Rfs*2)	c.1014_1023delTCCAAATTTT	.	chr10:89720862	18.26%	NM_000314.8	frameshift Deletion
SOS1	p.(N233Y)	c.697A>T	COSM95261	chr2:39281778	18.77%	NM_005633.4	missense
CTCF	p.(G318Qfs*16)	c.950_951dup	.	chr16:67646012	17.07%	NM_006565.4	frameshift Insertion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	46.67%	NM_000903.3	missense
MYO1B	p.(A1048V)	c.3143C>T	.	chr2:192279379	19.76%	NM_001130158.3	missense
PBRM1	p.(D633G)	c.1898A>G	.	chr3:52649393	12.17%	NM_018313.5	missense
IQCG	p.(I118L)	c.352A>C	.	chr3:197665582	19.21%	NM_001134435.2	missense
ERAP2	p.(F253V)	c.757T>G	.	chr5:96222401	11.20%	NM_001130140.2	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
CDKN1A	p.(R32H)	c.95G>A	.	chr6:36651973	8.90%	NM_078467.3	missense
ABCB1	p.(A947V)	c.2840C>T	.	chr7:87148729	16.35%	NM_000927.4	missense
POT1	p.(T12I)	c.35C>T	.	chr7:124532409	10.82%	NM_015450.3	missense
OR13D1	p.(S180F)	c.539C>T	.	chr9:107457241	17.92%	NM_001004484.1	missense
TSC1	p.(E860K)	c.2578G>A	.	chr9:135776149	20.36%	NM_000368.5	missense
INHBE	p.(A212T)	c.634G>A	.	chr12:57850212	18.17%	NM_031479.5	missense
PARP4	p.(?)	c.3285_3285+5delinsAGT	.	chr13:25021149	100.00%	NM_006437.4	unknown
DICER1	p.(R1736W)	c.5206C>T	.	chr14:95560383	8.10%	NM_030621.4	missense
TSC2	p.(S1704F)	c.5111C>T	.	chr16:2138091	17.97%	NM_000548.5	missense
SLX4	p.(A1811T)	c.5431G>A	.	chr16:3632417	4.55%	NM_032444.4	missense
SLX4	p.(S1608P)	c.4822T>C	.	chr16:3633429	47.97%	NM_032444.4	missense
ZNF507	p.(D851V)	c.2552A>T	.	chr19:32873679	16.55%	NM_014910.5	missense
KMT2B	p.(R1704L)	c.5111G>T	.	chr19:36221277	20.32%	NM_014727.3	missense
PLCG1	p.(G11C)	c.31G>T	.	chr20:39766312	47.60%	NM_002660.3	missense
NRK	p.(I342M)	c.1026A>G	.	chrX:105152236	17.53%	NM_198465.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0	0.53

Biomarker Descriptions

Microsatellite instability-High

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[15]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[16,17]. MSI is closely tied to the status of the mismatch repair (MMR) genes[18]. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[18]. 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[19]. 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)[19]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[20,21,22,23,24]. 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[17]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[16,17,21,25].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[16,17,26,27]. MSI-H is also observed in 5% of

Biomarker Descriptions (continued)

adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[26,27]. MSI-H is rare in pediatric solid tumors and is primarily observed in high grade gliomas, including astrocytoma and oligodendroglioma[28,29].

Potential relevance: Anti-PD-1 immune checkpoint inhibitor pembrolizumab[30] (2014) is approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[30] 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 in adults and children who have progressed following treatment, with no alternative options, making it the first anti-PD-1 inhibitor to be approved with a tumor-agnostic indication[30]. Dostarlimab[31] (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 therapy option in several cancer types that are dMMR/MSI-H such as advanced or metastatic colon or rectal cancer[22,32,33,34,35,36,37,38,39,40]. Nivolumab[41] (2015) is approved as a single agent or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[42] (2011), for adults and children with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[22,43,44]. 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[44]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors, compared to those with MSI-H tumors[45,46]. However, combining checkpoint blockade with chemotherapy or targeted therapies has demonstrated responses in MSS or pMMR cancers[45,46].

ESR1 p.(L536H) c.1607T>A

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[67,68]. Estrogen binding to ERα results in receptor dimerization, 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[69].

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[70,71,72,73]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[74,75,76,77,78].

Potential relevance: The FDA has approved elacestrant[79] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[33]. The FDA has also granted fast track designations to the following therapies: AC699[80] (2024) and lasofoxifene[81] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizaestrant[82] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[83] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[84] (1977), fulvestrant[85] (2002), letrozole[86] (1995), and exemestane[87] (2005) are FDA approved for ER-positive metastatic breast cancers[88,89]. 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[90,91,92].

ARID1A p.(Q1835*) c.5503C>T

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,93]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[93,94]. 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[94]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[94,95]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[93]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[93].

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[95]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[93]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[8,9,94]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[96].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[97], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[98], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

KMT2D p.(L2331Pfs*46) c.6991_6992insC

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[99]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[99]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[99].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

PIK3R1 p.(T576del) c.1727_1729delCGA

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[61]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[61]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[61]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[62,63]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[62,63,64,65]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[66]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[61].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[8]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[8].

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

PTEN p.(K267Rfs*9) c.800delA, PTEN p.(P339Rfs*2) c.1014_1023delTCCAAATTTT

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[47]. 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[48,49]. 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[50]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[51]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[52].

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[8,9]. 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[49,53,54,55,56]. 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[8,9].

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[57,58]. In 2022, the FDA granted fast track designation to the small molecule inhibitor,

Biomarker Descriptions (continued)

pidnarulex[59], 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[60] 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.

SOS1 p.(N233Y) c.697A>T

SOS Ras/Rac guanine nucleotide exchange factor 1

Background: The SOS1 gene encodes the SOS Ras/Rac guanine nucleotide exchange factor 1[1]. SOS1, along with isoform SOS2, are guanine nucleotide exchange factors (GEF) for Ras proteins, which activate Ras by catalyzing the exchange of GDP for GTP[10,11]. Hereditary mutations in SOS1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a genetic disorder in the group of RASopathies, which can lead to increased cancer risk[10].

Alterations and prevalence: Somatic mutations in SOS1 is observed in 10% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma and skin cutaneous melanoma, 4% of colorectal adenocarcinoma, and 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, and lung adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for SOS1 aberrations.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[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[2]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[3]. 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[4,5,6]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[7].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[8,9]. Biallelic loss of HLA-B is observed in 5% of DLBCL[8,9].

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

CTCF p.(G318Qfs*16) c.950_951dup

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[12]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[12,13,14]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[12].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[8,9].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. For the most up-to-date information, search www.fda.gov.

Microsatellite instability-High

dostarlimab

Cancer type: Rectal Cancer **Variant class:** Microsatellite instability-High

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the programmed death receptor-1 (PD-1)-blocking antibody, Jemperli (dostarlimab-gxly), for the treatment of patients with locally advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) rectal cancer.

Reference:

https://us.gsk.com//en-us/media/press-releases/jemperli-dostarlimab-gxly-receives-us-fda-breakthrough-therapy-designation-for-locally-advanced-dmmrmsi-h-rectal-cancer/

ATX-559

Cancer type: Colorectal Cancer **Variant class:** Microsatellite instability-High

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule DHX9 inhibitor, ATX-559, for the treatment of adult patients with unresectable/metastatic dMMR/MSI-H colorectal cancer post checkpoint inhibitor treatment.

Reference:

https://www.prnewswire.com/news-releases/accent-therapeutics-announces-first-patient-dosed-in-phase-12-trial-of-novel-kif18a-inhibitor-atx-295-and-receives-fda-fast-track-designation-for-lead-assets-atx-295-and-dhx9-inhibitor-atx-559-302427964.html

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-05-01. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

Microsatellite instability-High

pembrolizumab

Cancer type: Giant Cell Tumor of Soft Tissue **Variant class:** Microsatellite instability-High

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2025]

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS,

Genes Assayed (continued)

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

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

Microsatellite instability-High

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	◑	◑	◑	○	✖
nivolumab	○	◑	✖	✖	● (II)
ipilimumab + nivolumab	○	○	○	○	● (II)
dostarlimab	✖	◑	●	●	● (III)
avelumab	✖	◑	✖	✖	✖
cemiplimab	✖	○	✖	✖	✖
durvalumab + tremelimumab	✖	○	✖	✖	✖

* 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

Microsatellite instability-High (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nivolumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
nivolumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
retifanlimab	✖	○	✖	✖	✖
tislelizumab	✖	○	✖	✖	✖
toripalimab	✖	○	✖	✖	✖
dostarlimab + carboplatin + paclitaxel	✖	✖	●	✖	✖
anti-PD-L1 antibody, anti-PD-1, anti-CTLA-4, angiogenesis inhibitor	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II/III)
catequentinib, penpulimab	✖	✖	✖	✖	● (II)
catequentinib, tislelizumab	✖	✖	✖	✖	● (II)
dostarlimab, chemoradiation therapy	✖	✖	✖	✖	● (II)
dostarlimab, chemotherapy	✖	✖	✖	✖	● (II)
dostarlimab, radiation therapy	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
nivolumab, durvalumab	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
nivolumab, relatlimab	✖	✖	✖	✖	● (II)
nivolumab, rosiglitazone maleate, pembrolizumab, metformin hydrochloride	✖	✖	✖	✖	● (II)
tiragolumab, atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab, tiragolumab	✖	✖	✖	✖	● (I/II)
denileukin diftitox, pembrolizumab	✖	✖	✖	✖	● (I/II)
IDE-275	✖	✖	✖	✖	● (I/II)
INBRX-106, pembrolizumab	✖	✖	✖	✖	● (I/II)
invikafusp alfa (Marengo Therapeutics)	✖	✖	✖	✖	● (I/II)
MDNA-11, pembrolizumab	✖	✖	✖	✖	● (I/II)
NDI-219216	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

Microsatellite instability-High (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
NP-G2-044, anti-PD-1	✖	✖	✖	✖	● (I/II)
PRJ1-3024	✖	✖	✖	✖	● (I/II)
spartalizumab, pazopanib	✖	✖	✖	✖	● (I/II)
ST-067, obinutuzumab	✖	✖	✖	✖	● (I/II)
TT-702, anti-PD-1	✖	✖	✖	✖	● (I/II)
vusolimogene oderparepvec, nivolumab	✖	✖	✖	✖	● (I/II)
ABSK-043	✖	✖	✖	✖	● (I)
ATX-559	✖	✖	✖	✖	● (I)
CS-23546	✖	✖	✖	✖	● (I)
CVL-006	✖	✖	✖	✖	● (I)
HRO-761, tislelizumab, chemotherapy, pembrolizumab	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, ABBV-CLS-484, VEGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, natural killer cell therapy	✖	✖	✖	✖	● (I)
RO-7589831	✖	✖	✖	✖	● (I)
SG-001	✖	✖	✖	✖	● (I)

ESR1 p.(L536H) c.1607T>A

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

ARID1A p.(Q1835*) c.5503C>T

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***0.0%***
Not Detected	***Not Applicable***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 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.

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