Samkwang Medical Lab

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

Report Date: 15 Sep 2025

Patient Name:	고유희	**Primary Tumor Site:**	Colon
Gender:	F	**Collection Date:**	2025.08.20
Sample ID:	N25-199		

Sample Cancer Type: Colon Cancer

Table of Contents

Report Highlights

2 Relevant Biomarkers
20 Therapies Available
92 Clinical Trials

Relevant Colon Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK2	None detected
ERBB2	None detected	NTRK3	None detected
KRAS	None detected	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected

Genomic Alteration	Finding
Microsatellite Status	***Microsatellite instability-High***
Tumor Mutational Burden	***18.01 Mut/Mb measured***

HRD Status: ***HR Proficient (HRD-)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Microsatellite instability-High*	**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+	**dostarlimab** 2 / I, II+ **ipilimumab + nivolumab** 2 / I, II+ **pembrolizumab** 1, 2 / I, II+ **dostarlimab + chemotherapy** 2 cemiplimab I, II+ nivolumab I, II+ retifanlimab I, II+ tislelizumab I, II+ toripalimab I, II+ nivolumab + chemotherapy I pembrolizumab + chemotherapy I avelumab II+	80

* **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
			durvalumab + tremelimumab [II+]	
	Prognostic significance: NCCN: Good, ESMO: Very low			
IIC	*STRN::ALK fusion* striatin - ALK receptor tyrosine kinase Locus: chr2:37143221 - chr2:29446394	None*	**alectinib** [1, 2 / I, II+] **brigatinib** [1, 2 / I, II+] **ceritinib** [1, 2 / I, II+] **crizotinib** [1, 2 / I, II+] **ensartinib** [1 / I, II+] **lorlatinib** [1, 2 / I, II+] atezolizumab + bevacizumab + chemotherapy [II+]	13

* **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.

Alerts informed by public data sources: Contraindicated, Resistance, Breakthrough, Fast Track

Microsatellite instability-High	**ATX-559** [1]

Public data sources included in alerts: FDA1, NCCN, **EMA**2, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

*CDH1 p.(P126Rfs*89) c.377delC, EPHA2 p.(P460Rfs*33) c.1379delC, HLA-A deletion, HLA-B deletion, MGA p.(P893Lfs*40) c.2678delC, 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
CDH1	p.(P126Rfs*89)	c.377delC	.	chr16:68835780	17.88%	NM_004360.5	frameshift Deletion
EPHA2	p.(P460Rfs*33)	c.1379delC	COSM294351	chr1:16462198	28.08%	NM_004431.5	frameshift Deletion
MGA	p.(P893Lfs*40)	c.2678delC	.	chr15:42003136	10.79%	NM_001164273.1	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	49.05%	NM_000903.3	missense
PDE4B	p.(H446R)	c.1337A>G	.	chr1:66831402	3.90%	NM_002600.4	missense
DPYD	p.(N736T)	c.2207A>C	.	chr1:97770907	2.87%	NM_000110.4	missense
ODAPH	p.(?)	c.112-1G>A	.	chr4:76489323	17.21%	NM_001206981.2	unknown
INPP4B	p.(L585I)	c.1753C>A	.	chr4:143045881	3.18%	NM_001101669.3	missense
SLIT3	p.(K697E)	c.2089A>G	.	chr5:168176525	16.06%	NM_001271946.2	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
TAPBP	p.(P55S)	c.163C>T	.	chr6:33281516	44.03%	NM_172208.2	missense
HDAC2	p.(H29R)	c.86A>G	.	chr6:114281149	4.30%	NM_001527.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
RSPO3	p.(G209R)	c.625G>A	.	chr6:127476574	4.81%	NM_032784.5	missense
POT1	p.(R276K)	c.827G>A	.	chr7:124493068	42.49%	NM_015450.3	missense
NBN	p.(M152V)	c.454A>G	.	chr8:90992988	14.96%	NM_002485.5	missense
EFR3A	p.(N354K)	c.1062T>A	.	chr8:132982793	2.38%	NM_015137.6	missense
FAM135B	p.(L317M)	c.949C>A	.	chr8:139190858	7.45%	NM_015912.4	missense
LARP4B	p.(A632T)	c.1894G>A	.	chr10:860717	2.95%	NM_015155.3	missense
MAPK8	p.(N51H)	c.151A>C	.	chr10:49612923	15.50%	NM_139049.4	missense
A1CF	p.(A537T)	c.1609G>A	.	chr10:52569678	13.42%	NM_138932.2	missense
KMT2A	p.(A602D)	c.1805C>A	.	chr11:118343679	2.60%	NM_001197104.2	missense
PARP4	p.(A272V)	c.815C>T	.	chr13:25067798	15.82%	NM_006437.4	missense
TSHR	p.(L272R)	c.815T>G	.	chr14:81606145	17.48%	NM_000369.5	missense
AQP9	p.(S292N)	c.875G>A	.	chr15:58476321	49.03%	NM_020980.5	missense
FANCI	p.(A1175V)	c.3524C>T	.	chr15:89849412	4.96%	NM_001113378.2	missense
IGF1R	p.(A140G)	c.419C>G	.	chr15:99251115	12.40%	NM_000875.5	missense
TSC2	p.(V841A)	c.2522T>C	.	chr16:2124367	2.85%	NM_000548.5	missense
SLX4	p.(E46D)	c.138G>C	.	chr16:3658828	9.51%	NM_032444.4	missense
CREBBP	p.(R1800W)	c.5398C>T	.	chr16:3779650	5.00%	NM_004380.3	missense
CDK12	p.(R331Q)	c.992G>A	.	chr17:37619316	2.75%	NM_016507.4	missense
GNA13	p.(R81H)	c.242G>A	.	chr17:63052470	17.91%	NM_006572.6	missense
SMAD2	p.(R337C)	c.1009C>T	.	chr18:45372160	4.20%	NM_001003652.4	missense
STK11	p.(P413T)	c.1237C>A	.	chr19:1226581	4.42%	NM_000455.5	missense
JAK3	p.(H116P)	c.347A>C	.	chr19:17954262	3.42%	NM_000215.4	missense
ZNF568	p.(S612R)	c.1834A>C	.	chr19:37488427	17.84%	NM_001204838.1	missense
PTPRT	p.(R1337H)	c.4010G>A	.	chr20:40714387	15.65%	NM_133170.4	missense
RUNX1	p.(L313I)	c.937C>A	.	chr21:36171628	22.21%	NM_001754.5	missense
BCOR	p.(K802E)	c.2404A>G	.	chrX:39932195	19.25%	NM_001123385.2	missense
RBM10	p.(P162T)	c.484C>A	.	chrX:47030514	18.26%	NM_001204468.1	missense
STAG2	p.(P1077L)	c.3230C>T	.	chrX:123220573	16.29%	NM_001042749.2	missense

Gene Fusions

Genes	Variant ID	Locus
STRN::ALK	STRN-ALK.S3A20.COSF1430	chr2:37143221 - chr2:29446394

Variant Details (continued)

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-A	chr6:29910229	0	0.51
HLA-B	chr6:31322252	0	0.46

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[17]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[18,19]. MSI is closely tied to the status of the mismatch repair (MMR) genes[20]. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[20]. 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[21]. 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)[21]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[22,23,24,25,26]. 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[19]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[18,19,23,27].

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[18,19,28,29]. 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[28,29]. MSI-H is rare in pediatric solid tumors and is primarily observed in high grade gliomas, including astrocytoma and oligodendroglioma[30,31].

Potential relevance: Anti-PD-1 immune checkpoint inhibitor pembrolizumab[32] (2014) is approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[32] 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[32]. Dostarlimab[33] (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[24,34,35,36,37,38,39,40,41,42]. Nivolumab[43] (2015) is approved as a single agent or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[44] (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[24,45,46]. 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[46]. 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[47,48]. However, combining checkpoint blockade with chemotherapy or targeted therapies has demonstrated responses in MSS or pMMR cancers[47,48].

STRN::ALK fusion

ALK receptor tyrosine kinase, striatin

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK), which has sequence similarity to the insulin receptor subfamily of kinases[53]. ALK is frequently altered in cancer, most commonly through chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with various partner genes[54]. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways[54,55,56,57].

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin 1 (NPM1) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of adult and over 80% of pediatric anaplastic large cell lymphoma (ALCL) cases[53,58,59]. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1[60,61,62]. Notably, ALK F1174L, F1245C, and R1275Q mutations are found in over 80% of ALK-mutated

Biomarker Descriptions (continued)

neuroblastoma[63]. ALK mutations have also been reported in 5% of pediatric soft tissue sarcomas and less than 1.5% of other solid and hematological malignancies, including peripheral nervous system tumors, gliomas, leukemia, and bone cancer[8,9].

Potential relevance: The first-generation small molecule tyrosine kinase inhibitor (TKI), crizotinib[64], was FDA approved (2011) for the treatment of adults with ALK-positive advanced NSCLC, as well as pediatric and adult populations with ALK-positive ALCL or inflammatory myofibroblastic tumor (IMT). ALK fusions are a diagnostic marker of infant-type hemispheric glioma and ALK-rearranged renal cell carcinoma[65,66,67]. Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants, have been shown to confer acquired resistance to crizotinib in ALK-positive NSCLC[68,69,70,71]. Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R[72]. In order to overcome acquired resistance, second- and third-generation ALK inhibitors including ceritinib[73] (2014), alectinib[74] (2015), brigatinib[75] (2017), lorlatinib[76] (2018), and ensartinib[77] (2024) were developed and approved for adults by the FDA. The FDA granted breakthrough therapy designation (2024) to NVL-655[78] for locally advanced or metastatic ALK-positive NSCLC patients who have been previously treated with two or more ALK TKIs.

CDH1 p.(P126Rfs*89) c.377delC

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,10]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[11]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[12,13]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[14].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[8,9,15,16]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[8,9]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

EPHA2 p.(P460Rfs*33) c.1379delC

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[79,80]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[80]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[79,80].

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[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,

Biomarker Descriptions (continued)

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-A[7].

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[8,9]. Biallelic loss of HLA-A is observed in 4% of DLBCL[8,9].

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

MGA p.(P893Lfs*40) c.2678delC

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[1,49]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[50]. 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[49]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[51]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[52].

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[8,9]. 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[8,9].

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[52].

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

STRN::ALK fusion

neladalkib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to a brain-penetrant ALK-selective tyrosine kinase inhibitor (TKI), NVL-655, for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have been previously treated with two or more ALK TKIs.

Reference:

https://investors.nuvalent.com/2024-05-16-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-655

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	◐	◐	◐	◐	● (III)
ipilimumab + nivolumab	●	◐	◐	●	● (II)
nivolumab	●	◐	✖	✖	● (II)
dostarlimab	✖	◐	○	○	● (III)
cemiplimab	✖	◐	✖	✖	● (II)
tislelizumab	✖	◐	✖	✖	● (II)
retifanlimab	✖	◐	✖	✖	✖

* 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*
toripalimab	✖	◐	✖	✖	✖
avelumab	✖	○	✖	✖	✖
durvalumab + tremelimumab	✖	○	✖	✖	✖
nivolumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
nivolumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
dostarlimab + carboplatin + paclitaxel	✖	✖	○	✖	✖
anti-PD-1, anti-PD-L1 antibody, anti-CTLA-4	✖	✖	✖	✖	● (III)
anti-PD-L1 antibody, anti-PD-1, anti-CTLA-4, angiogenesis inhibitor	✖	✖	✖	✖	● (III)
ipilimumab (Innovent Biologics), sintilimab	✖	✖	✖	✖	● (III)
nivolumab, encorafenib, binimetinib, cetuximab	✖	✖	✖	✖	● (III)
nivolumab, ipilimumab	✖	✖	✖	✖	● (III)
PSB-205	✖	✖	✖	✖	● (III)
sintilimab	✖	✖	✖	✖	● (III)
tislelizumab, chemotherapy	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II/III)
anti-PD-1, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, anti-PD-1	✖	✖	✖	✖	● (II)
botensilimab, balstilimab	✖	✖	✖	✖	● (II)
botensilimab, balstilimab + botensilimab	✖	✖	✖	✖	● (II)
cadonilimab	✖	✖	✖	✖	● (II)
catequentinib, penpulimab	✖	✖	✖	✖	● (II)
catequentinib, tislelizumab	✖	✖	✖	✖	● (II)
cemiplimab, fianlimab	✖	✖	✖	✖	● (II)
dostarlimab, chemoradiation therapy	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
envafolimab	✖	✖	✖	✖	● (II)
KN046, regorafenib, apatinib	✖	✖	✖	✖	● (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*
nivolumab, durvalumab	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab, radiation therapy	✖	✖	✖	✖	● (II)
nivolumab, relatlimab	✖	✖	✖	✖	● (II)
nivolumab, rosiglitazone maleate, pembrolizumab, metformin hydrochloride	✖	✖	✖	✖	● (II)
olaparib, pembrolizumab	✖	✖	✖	✖	● (II)
pembrolizumab, regorafenib	✖	✖	✖	✖	● (II)
sintilimab, ipilimumab (Innovent Biologics), lenvatinib, anti-PD-1, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
tinodasertib, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
tiragolumab, atezolizumab	✖	✖	✖	✖	● (II)
toripalimab, celecoxib	✖	✖	✖	✖	● (II)
AFM-24_I, atezolizumab	✖	✖	✖	✖	● (I/II)
alintegimod, ipilimumab, nivolumab	✖	✖	✖	✖	● (I/II)
atezolizumab, pelareorep	✖	✖	✖	✖	● (I/II)
BR-790, tislelizumab	✖	✖	✖	✖	● (I/II)
celecoxib, toripalimab	✖	✖	✖	✖	● (I/II)
chemotherapy, KSQ-004, aldesleukin	✖	✖	✖	✖	● (I/II)
chemotherapy, leucovorin, pembrolizumab	✖	✖	✖	✖	● (I/II)
denileukin diftitox, pembrolizumab	✖	✖	✖	✖	● (I/II)
EU-101	✖	✖	✖	✖	● (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)
NEO-212, pembrolizumab, nivolumab	✖	✖	✖	✖	● (I/II)
NP-G2-044, anti-PD-1	✖	✖	✖	✖	● (I/II)
PRJ1-3024	✖	✖	✖	✖	● (I/II)
spartalizumab, pazopanib	✖	✖	✖	✖	● (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*
ST-067, obinutuzumab	✖	✖	✖	✖	● (I/II)
ST-316, fruquintinib, bevacizumab, chemotherapy	✖	✖	✖	✖	● (I/II)
toripalimab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (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)
interferon alpha (Werewolf Therapeutics), pembrolizumab	✖	✖	✖	✖	● (I)
NWY-001	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, ABBV-CLS-484, VEGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, natural killer cell therapy	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, umbilical cord blood NK cells	✖	✖	✖	✖	● (I)
pembrolizumab, KFA115	✖	✖	✖	✖	● (I)
RO-7589831	✖	✖	✖	✖	● (I)
SG-001	✖	✖	✖	✖	● (I)

STRN::ALK fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alectinib	○	○	○	○	● (II/III)
brigatinib	○	○	○	○	● (II)
crizotinib	○	○	○	○	● (I)
ceritinib	○	○	○	○	✖
lorlatinib	○	○	○	○	✖
ensartinib	○	○	✖	✖	✖

* 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

STRN::ALK fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	○	✖
alectinib, crizotinib	✖	✖	✖	✖	● (II)
furetinib	✖	✖	✖	✖	● (I/II)
neladalkib	✖	✖	✖	✖	● (I/II)
LZ-001	✖	✖	✖	✖	● (I)
talazoparib, crizotinib	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***4.84%***
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.

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
3. 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
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
7. 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
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. 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
10. Halbleib et al. Cadherins in development: cell adhesion, sorting, and tissue morphogenesis. Genes Dev. 2006 Dec 1;20(23):3199-214. PMID: 17158740
11. Pećina-Slaus. Tumor suppressor gene E-cadherin and its role in normal and malignant cells. Cancer Cell Int. 2003 Oct 14;3(1):17. PMID: 14613514
12. Hirohashi. Inactivation of the E-cadherin-mediated cell adhesion system in human cancers. Am J Pathol. 1998 Aug;153(2):333-9. PMID: 9708792
13. Bruner et al. Loss of E-Cadherin-Dependent Cell-Cell Adhesion and the Development and Progression of Cancer. Cold Spring Harb Perspect Biol. 2018 Mar 1;10(3). PMID: 28507022
14. Adib et al. CDH1 germline variants are enriched in patients with colorectal cancer, gastric cancer, and breast cancer. Br J Cancer. 2022 Mar;126(5):797-803. PMID: 34949788
15. Al-Ahmadie et al. Frequent somatic CDH1 loss-of-function mutations in plasmacytoid variant bladder cancer. Nat Genet. 2016 Apr;48(4):356-8. PMID: 26901067
16. Kim et al. Loss of CDH1 (E-cadherin) expression is associated with infiltrative tumour growth and lymph node metastasis. Br J Cancer. 2016 Jan 19;114(2):199-206. PMID: 26742007
17. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
18. 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
19. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
20. 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
21. 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
22. 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
23. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
24. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
25. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
26. 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
27. 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
28. 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
29. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653

References (continued)

30. Yoshida et al. Microsatellite instability-high is rare events in refractory pediatric solid tumors. Pediatr Hematol Oncol. 2022 Aug;39(5):468-474. PMID: 34964684
31. Klein et al. Vascular wall-resident CD44+ multipotent stem cells give rise to pericytes and smooth muscle cells and contribute to new vessel maturation. PLoS One. 2011;6(5):e20540. PMID: 21637782
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
34. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
35. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2025]
36. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2025]
37. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
38. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 3.2025]
39. NCCN Guidelines® - NCCN-Hepatocellular Carcinoma [Version 1.2025]
40. NCCN Guidelines® - NCCN-Biliary Tract Cancers [Version 1.2025]
41. NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2025]
42. NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2025]
43. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
45. 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
46. 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
47. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
48. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
49. Hurlin et al. The MAX-interacting transcription factor network. Semin. Cancer Biol. 2006 Aug;16(4):265-74. PMID: 16908182
50. Susan. An Overview of the Basic Helix-Loop-Helix Proteins. Genome Biol. 2004;5(6):226. PMID: 15186484
51. 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
52. 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
53. Webb et al. Anaplastic lymphoma kinase: role in cancer pathogenesis and small-molecule inhibitor development for therapy. Expert Rev Anticancer Ther. 2009 Mar;9(3):331-56. PMID: 19275511
54. Shaw et al. Tyrosine kinase gene rearrangements in epithelial malignancies. Nat. Rev. Cancer. 2013 Nov;13(11):772-87. PMID: 24132104
55. Chiarle et al. Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. Nat. Med. 2005 Jun;11(6):623-9. PMID: 15895073
56. Bai et al. Nucleophosmin-anaplastic lymphoma kinase associated with anaplastic large-cell lymphoma activates the phosphatidylinositol 3-kinase/Akt antiapoptotic signaling pathway. Blood. 2000 Dec 15;96(13):4319-27. PMID: 11110708
57. Hrustanovic et al. RAS signaling in ALK fusion lung cancer. Small GTPases. 2016;7(1):32-3. PMID: 26901483
58. Morris et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994 Mar 4;263(5151):1281-4. PMID: 8122112
59. Shreenivas et al. ALK fusions in the pan-cancer setting: another tumor-agnostic target?. NPJ Precis Oncol. 2023 Sep 29;7(1):101. PMID: 37773318
60. Kwak et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N. Engl. J. Med. 2010 Oct 28;363(18):1693-703. PMID: 20979469
61. Yu et al. Frequencies of ALK rearrangements in lung adenocarcinoma subtypes: a study of 2299 Chinese cases. Springerplus. 2016 Jun 27;5(1):894. doi: 10.1186/s40064-016-2607-5. eCollection 2016. PMID: 27386342

References (continued)

62. Dai et al. Incidence and patterns of ALK FISH abnormalities seen in a large unselected series of lung carcinomas. Send to Mol Cytogenet. 2012 Dec 3;5(1):44. doi: 10.1186/1755-8166-5-44. PMID: 23198868
63. Rosswog et al. Genomic ALK alterations in primary and relapsed neuroblastoma. Br J Cancer. 2023 Apr;128(8):1559-1571. PMID: 36807339
64. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202570s036lbl.pdf
65. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]
66. Mossé. Anaplastic Lymphoma Kinase as a Cancer Target in Pediatric Malignancies. Clin Cancer Res. 2016 Feb 1;22(3):546-52. PMID: 26503946
67. Zhang et al. Genomic alterations and diagnosis of renal cancer. Virchows Arch. 2024 Feb;484(2):323-337. PMID: 37999735
68. Choi et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N. Engl. J. Med. 2010 Oct 28;363(18):1734-9. PMID: 20979473
69. Awad et al. ALK inhibitors in non-small cell lung cancer: crizotinib and beyond. Clin Adv Hematol Oncol. 2014 Jul;12(7):429-39. PMID: 25322323
70. Kim et al. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. J Thorac Oncol. 2013 Apr;8(4):415-22. PMID: 23344087
71. Katayama et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Sci Transl Med. 2012 Feb 8;4(120):120ra17. doi: 10.1126/scitranslmed.3003316. Epub 2012 Jan 25. PMID: 22277784
72. Katayama. Drug resistance in anaplastic lymphoma kinase-rearranged lung cancer. Cancer Sci. 2018 Mar;109(3):572-580. PMID: 29336091
73. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf
74. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208434s015lbl.pdf
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208772s013lbl.pdf
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf
77. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218171s000lbl.pdf
78. https://investors.nuvalent.com/2024-05-16-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-655
79. Tan et al. EPHA2 mutations with oncogenic characteristics in squamous cell lung cancer and malignant pleural mesothelioma. Oncogenesis. 2019 Sep 4;8(9):49. PMID: 31484920
80. Tandon et al. Emerging strategies for EphA2 receptor targeting for cancer therapeutics. Expert Opin Ther Targets. 2011 Jan;15(1):31-51. PMID: 21142802