

Patient Name: 이재연  
Gender: M  
Sample ID: N25-352

Primary Tumor Site: lung  
Collection Date: 2025.11.27

## Sample Cancer Type: Lung Cancer

Table of Contents	Page
Variant Details	2
Biomarker Descriptions	3
Alert Details	6
Relevant Therapy Summary	11

Report Highlights  
1 Relevant Biomarkers  
1 Therapies Available  
4 Clinical Trials

## Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

  

Genomic Alteration	Finding
Tumor Mutational Burden	11.36 Mut/Mb measured

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIIC	NRAS p.(G12C) c.34G>T  NRAS proto-oncogene, GTPase Allele Frequency: 7.99% Locus: chr1:115258748 Transcript: NM_002524.5	None*	bevacizumab + chemotherapy <sup>1</sup>	4

\* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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

Microsatellite stable, PTEN p.(A148Gfs\*32) c.442\_443insG, TP53 p.(R249M) c.746G>T, YAP1 amplification, FAT1 p.(E2056\*) c.6166G>T, Tumor Mutational Burden

## Variant Details

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NRAS	p.(G12C)	c.34G>T	COSM562	chr1:115258748	7.99%	NM_002524.5	missense
PTEN	p.(A148Gfs*32)	c.442_443insG	.	chr10:89692956	7.67%	NM_000314.8	frameshift Insertion
TP53	p.(R249M)	c.746G>T	COSM43871	chr17:7577535	7.60%	NM_000546.6	missense
FAT1	p.(E2056*)	c.6166G>T	.	chr4:187541574	12.86%	NM_005245.4	nonsense
EPS8L3	p.(L383M)	c.1147C>A	.	chr1:110295795	8.99%	NM_139053.3	missense
CNTNAP5	p.(T765N)	c.2294C>A	.	chr2:125521311	8.59%	NM_130773.4	missense
PP2D1	p.(M240*)	c.718delA	.	chr3:20042893	45.61%	NM_001252657.2	nonsense
MAML3	p.(Q500_Q504delinsR)	c.1455_1511delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGCAGCAinsGCAGCA ACAGCAACAGCAGCA GCAGCAGCAGCAGCA GCAACAGCG	.	chr4:140811079	1.38%	NM_018717.5	nonframeshift Block Substitution
MAML3	p.(Q507_Q510del)	c.1455_1506delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACAGC AACAGCAGCAGCAGC AGCAGCAGCAGCAA	.	chr4:140811084	98.62%	NM_018717.5	nonframeshift Block Substitution
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	62.28%	NM_002439.5	nonframeshift Insertion
SLC15A4	p.(A419V)	c.1256C>T	.	chr12:129293335	12.26%	NM_145648.4	missense
TSC2	p.(G1117E)	c.3350G>A	.	chr16:2129623	2.86%	NM_000548.5	missense
TSC2	p.(P1444H)	c.4331C>A	.	chr16:2134554	50.08%	NM_000548.5	missense
JAK3	p.(L1035M)	c.3103C>A	.	chr19:17941021	10.42%	NM_000215.4	missense
KMT2B	p.(V715F)	c.2143G>T	.	chr19:36212392	9.20%	NM_014727.3	missense
RBM10	p.(?)	c.1097-1G>T	.	chrX:47039278	21.40%	NM_001204468.1	unknown
TEX11	p.(Q472L)	c.1415A>T	.	chrX:69890237	5.38%	NM_001003811.2	missense

### Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
YAP1	chr11:101981594	65.25	13.65

## Biomarker Descriptions

### NRAS p.(G12C) c.34G>T

*NRAS proto-oncogene, GTPase*

**Background:** The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS<sup>17</sup>. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival<sup>69,70,71</sup>. Recurrent mutations in RAS lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features<sup>72</sup>. Point mutations in NRAS are also observed in several cancers including melanoma, characterized by thick tumors, increased tumor recurrence, treatment resistance, and increased mitosis<sup>73</sup>.

**Alterations and prevalence:** NRAS mutations are observed in 29% of skin cutaneous melanoma, 8% of acute myeloid leukemia and thyroid carcinoma, 6% of colorectal adenocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of testicular germ cell tumors and cholangiocarcinoma, and 2% of thymoma, bladder urothelial carcinoma, uterine carcinosarcoma, and kidney chromophobe<sup>7,8,74</sup>. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61<sup>7,8,75</sup>. Mutations at A59, K117, and A146 have also been observed but are less frequent<sup>7,76</sup>. Alterations in NRAS are also observed in pediatric cancers<sup>7</sup>. Somatic mutation in NRAS are observed in 16% of leukemia (57 in 354 cases), 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of soft tissue sarcoma (3 in 38 cases), and less than 1% of glioma (2 in 297 cases), bone cancer (2 in 327 cases), and embryonal tumors (1 in 332 cases)<sup>7</sup>.

**Potential relevance:** Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab<sup>77</sup> and panitumumab<sup>78</sup>, are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)<sup>76</sup>. In 2022, the FDA granted fast track designation to the pan-RAF inhibitor, KIN-278<sup>79</sup>, for the treatment of NRAS-mutant metastatic or unresectable melanoma. In 2023, the FDA granted fast track designation to the pan-RAF inhibitor, nafarafenib, in combination with trametinib<sup>80</sup> for NRAS-mutated unresectable or metastatic melanoma. In 2024, the FDA granted fast track designation to the MAPK pathway inhibitor, IMM-1-104<sup>81</sup>, for the treatment of NRAS-mutant metastatic or unresectable melanoma. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome<sup>40</sup> as well as melanoma<sup>82</sup>. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively<sup>83</sup>.

### 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<sup>46</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>47,48</sup>. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>49</sup>. 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<sup>50</sup>. 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)<sup>50</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>51,52,53,54,55</sup>. 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<sup>48</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>47,48,52,56</sup>.

**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<sup>47,48,57,58</sup>. 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<sup>57,58</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>59</sup> (2014) and nivolumab<sup>60</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>59</sup> 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<sup>59</sup>. Dostarlimab<sup>61</sup> (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<sup>53,62</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>63</sup> (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<sup>53,64,65</sup>. 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<sup>65</sup>. 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

## Biomarker Descriptions (continued)

with MSI-H tumors<sup>66,67</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>66,67</sup>.

### PTEN p.(A148Gfs\*32) c.442\_443insG

*phosphatase and tensin homolog*

**Background:** The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities<sup>1</sup>. 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<sup>2,3</sup>. 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<sup>4</sup>. 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<sup>5</sup>. PTEN germline mutations are also associated with inherited cancer risk in several cancer types<sup>6</sup>.

**Alterations and prevalence:** PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are observed in several cancers including 65% of uterine cancer, 34% of uterine corpus endometrial carcinoma, 20% of uterine carcinosarcoma, 11% of lung squamous cell carcinoma, and 5-10% of skin cutaneous melanoma, kidney chromophobe, stomach adenocarcinoma, stomach squamous cell carcinoma, and cervical squamous cell carcinoma<sup>7,8</sup>. 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<sup>3,9,10,11,12</sup>. PTEN gene deletion is observed in several cancers including 17% of prostate adenocarcinoma, 10% of lung squamous cell carcinoma and glioblastoma multiforme, 7% of skin cutaneous melanoma, 6% of diffuse large B-cell lymphoma, sarcoma, and 1-5% of breast invasive carcinoma, melanoma, sarcoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, and uterine corpus endometrial carcinoma<sup>7,8</sup>. Alterations in PTEN are also observed in pediatric cancers<sup>7</sup>. Somatic mutations in PTEN are observed in 10% of T-lymphoblastic leukemia/lymphoma (4 in 41 cases), 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of glioma (7 in 297 cases), and 1% of bone cancer (4 in 327 cases) and embryonal tumors (4 in 332 cases)<sup>7</sup>. Biallelic deletion of PTEN is observed in 6% of glioma (1 in 16 cases), 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (10 in 250 cases), and less than 1% of embryonal tumors (5 in 731 cases)<sup>7</sup>. Structural alterations in PTEN are observed in less than 1% of bone cancer (1 in 150 cases)<sup>7</sup>.

**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<sup>13,14</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>15</sup>, 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<sup>16</sup> 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.

### TP53 p.(R249M) c.746G>T

*tumor protein p53*

**Background:** The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair<sup>17</sup>. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis<sup>23</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>24</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>25,26</sup>.

**Alterations and prevalence:** TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)<sup>7,8,27,28,29,30</sup>. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282<sup>7,8</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>31,32,33,34</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>7,8</sup>. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)<sup>7,8</sup>. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)<sup>7,8</sup>.

**Potential relevance:** The small molecule p53 reactivator, PC14586<sup>35</sup> (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation<sup>36,37</sup>. TP53 mutations are a diagnostic marker of SHH-

## Biomarker Descriptions (continued)

activated, TP53-mutant medulloblastoma<sup>38</sup>. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)<sup>39,40,41,42,43</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>44</sup>. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system<sup>45</sup>.

### **YAP1 amplification**

*Yes associated protein 1*

Background: The YAP1 gene encodes the Yes1 associated transcriptional regulator<sup>17</sup>. YAP1 functions as a transcriptional coactivator for TEAD transcription factors and is an important effector of the Hippo signaling pathway<sup>18</sup>. The Hippo pathway is considered a tumor suppressor pathway due to its involvement in various cellular processes including cell proliferation, apoptosis, stem cell expansion, and negative regulation of YAP1<sup>18,19</sup>. Aberrations in YAP1, including upregulation, have been associated with tumorigenesis and shorter survival<sup>19,20</sup>. Germline mutations, specifically R331W, have been associated with an increased risk for lung adenocarcinoma<sup>21</sup>.

Alterations and prevalence: Somatic mutations in YAP1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of skin cutaneous melanoma, esophageal adenocarcinoma, kidney chromophobe, and 1% of uveal melanoma, kidney renal papillary cell carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and colorectal adenocarcinoma<sup>7,8</sup>. Amplification of YAP1 is observed in 10% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and ovarian cystadenocarcinoma, and 3% of bladder urothelial carcinoma, sarcoma, and esophageal adenocarcinoma<sup>7,8</sup>. YAP1 fusions are observed in 1% of sarcoma, esophageal adenocarcinoma, cervical squamous cell carcinoma, skin cutaneous melanoma, and head and neck squamous cell carcinoma<sup>7,8</sup>.

Potential relevance: Currently, no therapies are approved for YAP1 aberrations. YAP1::TFE3 fusion is considered an ancillary diagnostic marker for epithelioid hemangioendothelioma<sup>22</sup>. Overexpression of YAP1 is a poor prognostic marker in hepatocellular carcinoma, gastric cancer, colorectal cancer, non-small cell lung cancer, and small cell lung cancer<sup>18</sup>.

### **FAT1 p.(E2056\*) c.6166G>T**

*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<sup>17,68</sup>. 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<sup>68</sup>. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion<sup>68</sup>. 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<sup>68</sup>. Alterations of FAT1 lead to downregulation or loss of function, supporting a tumor suppressor role for FAT1<sup>68</sup>.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot<sup>7,8</sup>. 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<sup>7,8</sup>. 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<sup>7,8</sup>.

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

## Alerts Informed By Public Data Sources

### Current FDA Information

 Contraindicated

 Not recommended

 Resistance

 Breakthrough

 Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

#### NRAS p.(G12C) c.34G>T

##### cetuximab

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: NRAS G12 mutation

##### Indications and usage:

Erbxitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

##### Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

##### Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

##### BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

- in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

##### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125084s279lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf)

## NRAS p.(G12C) c.34G>T (continued)

### 🚫 panitumumab

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: NRAS G12 mutation

#### Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of:

Adult patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test) Metastatic Colorectal Cancer (mCRC)\*:

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)\*

- In combination with sotorasib, for the treatment of adult patients with KRAS G12C-mutated mCRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

\*Limitations of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC unless used in combination with sotorasib in KRAS G12C-mutated mCRC. VECTIBIX® is not indicated for the treatment of patients with mCRC for whom RAS mutation status is unknown.

#### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125147s213lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf)

## Current NCCN Information

🚫 Contraindicated

⊖ Not recommended

🛡 Resistance

🚀 Breakthrough

🅰️ Fast Track

NCCN information is current as of 2025-11-03. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org).

For NCCN International Adaptations & Translations, search [www.nccn.org/global/what-we-do/international-adaptations](https://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.

All guidelines cited below are referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) National Comprehensive Cancer Network, Inc. 2023. All rights reserved. NCCN makes no warranties regarding their content.

## NRAS p.(G12C) c.34G>T

### 🚫 cetuximab

Cancer type: Colon Cancer

Variant class: NRAS G12 mutation

#### Summary:

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

- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]

## NRAS p.(G12C) c.34G>T (continued)

### 🚫 cetuximab

Cancer type: Rectal Cancer

Variant class: NRAS G12 mutation

**Summary:**

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

- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

### 🚫 panitumumab

Cancer type: Colon Cancer

Variant class: NRAS G12 mutation

**Summary:**

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

- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]

### 🚫 panitumumab

Cancer type: Rectal Cancer

Variant class: NRAS G12 mutation

**Summary:**

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

- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

## Current EMA Information

🚫 Contraindicated

🚫 Not recommended

🚫 Resistance

🚀 Breakthrough

🅰️ Fast Track

EMA information is current as of 2025-11-25. For the most up-to-date information, search [www.ema.europa.eu](http://www.ema.europa.eu).

## NRAS p.(G12C) c.34G>T

### 🚫 cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: NRAS G12 mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf)

## NRAS p.(G12C) c.34G>T (continued)

### 🚫 panitumumab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2025-05-07

Variant class: NRAS G12 mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf)

## Current ESMO Information

🚫 Contraindicated

➡ Not recommended

➡ Resistance

➡ Breakthrough

➡ Fast Track

ESMO information is current as of 2025-11-03. For the most up-to-date information, search [www.esmo.org](http://www.esmo.org).

## NRAS p.(G12C) c.34G>T

### 🚫 cetuximab

Cancer type: Colorectal Cancer

Variant class: NRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

### 🚫 panitumumab

Cancer type: Colorectal Cancer

Variant class: NRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

## 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,

## Genes Assayed (continued)

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

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, SLC01B3, SMC1A, SMO, SNCAP, 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, CBF, 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, FANC, 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, 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, SLC01B3, 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, 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, RSP02, RSP03, 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, CBF, 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, FANC, FANCG, FANCI, 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     
 X No evidence

### NRAS p.(G12C) c.34G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	X	X	X	O	X
bevacizumab + FOLFIRI	X	X	X	O	X
bevacizumab + FOLFOX	X	X	X	O	X
bevacizumab + FOLFOXIRI	X	X	X	O	X
daraxonrasib	X	X	X	X	● (III)
ERAS-0015	X	X	X	X	● (I/II)
Nest-1	X	X	X	X	● (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	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 (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-11-25. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-11-03. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-11-25. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://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. 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
2. 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
3. Chalhoub et al. PTEN and the PI3-kinase pathway in cancer. *Annu Rev Pathol.* 2009;4:127-50. PMID: 18767981
4. 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
5. Leslie et al. Inherited PTEN mutations and the prediction of phenotype. *Semin. Cell Dev. Biol.* 2016 Apr;52:30-8. PMID: 26827793
6. Tan et al. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin. Cancer Res.* 2012 Jan 15;18(2):400-7. PMID: 22252256
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. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. Dillon et al. Therapeutic targeting of cancers with loss of PTEN function. *Curr Drug Targets.* 2014 Jan;15(1):65-79. PMID: 24387334
10. 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
11. Kato et al. Functional evaluation of p53 and PTEN gene mutations in gliomas. *Clin. Cancer Res.* 2000 Oct;6(10):3937-43. PMID: 11051241
12. 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
13. 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
14. 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
15. <https://www.senhwabio.com//en/news/20220125>
16. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/218197s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf)
17. 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
18. Shibata et al. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. *Int J Cancer.* 2018 Nov 1;143(9):2133-2144. PMID: 29696628
19. Fernandez-L et al. YAP1 is amplified and up-regulated in hedgehog-associated medulloblastomas and mediates Sonic hedgehog-driven neural precursor proliferation. *Genes Dev.* 2009 Dec 1;23(23):2729-41. PMID: 19952108
20. Liu et al. Clinical significance of yes-associated protein overexpression in cervical carcinoma: the differential effects based on histotypes. *Int J Gynecol Cancer.* 2013 May;23(4):735-42. PMID: 23502453
21. Chen et al. R331W Missense Mutation of Oncogene YAP1 Is a Germline Risk Allele for Lung Adenocarcinoma With Medical Actionability. *J Clin Oncol.* 2015 Jul 10;33(20):2303-10. PMID: 26056182
22. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
23. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013 Jul;27(4):254-71. PMID: 23885265
24. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell.* 2014 Mar 17;25(3):304-17. PMID: 24651012
25. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol.* 2010 Jan;2(1):a001008. PMID: 20182602
26. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med.* 2017 Apr 3;7(4). PMID: 28270529
27. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25. PMID: 22960745
28. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
29. 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

## References (continued)

30. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
31. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum. Mutat.* 2002 Jun;19(6):607-14. PMID: 12007217
32. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes Cancer*. 2011 Apr;2(4):466-74. PMID: 21779514
33. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*. 2007 Apr 2;26(15):2157-65. PMID: 17401424
34. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. *Hum. Mutat.* 2014 Jun;35(6):766-78. PMID: 24729566
35. <https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html>
36. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. *Front Oncol.* 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
37. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165
38. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. PMID: 34185076
39. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
40. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
41. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
42. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
43. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
44. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
45. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat. Med.* 2020 Aug 3. PMID: 32747829
46. Lander et al. Initial sequencing and analysis of the human genome. *Nature*. 2001 Feb 15;409(6822):860-921. PMID: 11237011
47. 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
48. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
49. 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
50. 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
51. 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
52. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis*. 2008 Apr;29(4):673-80. PMID: 17942460
53. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
54. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers*. 2004;20(4-5):199-206. PMID: 15528785
55. 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
56. 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
57. 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
58. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
59. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125514s178lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf)

## References (continued)

60. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125554s131lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf)
61. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/761174s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf)
62. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
63. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125377s136lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf)
64. 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
65. 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
66. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
67. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
68. Peng et al. Role of FAT1 in health and disease. *Oncol Lett.* 2021 May;21(5):398. PMID: 33777221
69. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
70. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
71. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
72. Runtuwene et al. Noonan syndrome gain-of-function mutations in NRAS cause zebrafish gastrulation defects. *Dis Model Mech.* 2011 May;4(3):393-9. PMID: 21263000
73. Feichtenschlager et al. Suppression of NRAS-mutant melanoma growth with NRAS-targeting Antisense Oligonucleotide treatment reveals therapeutically relevant kinase co-dependencies. *Commun Med (Lond).* 2025 Jun 5;5(1):216. PMID: 40473796
74. Janku et al. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. *PLoS ONE.* 2011;6(7):e22769. PMID: 21829508
75. Ohashi et al. Characteristics of lung cancers harboring NRAS mutations. *Clin. Cancer Res.* 2013 May 1;19(9):2584-91. PMID: 23515407
76. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J. Clin. Oncol.* 2016 Jan 10;34(2):179-85. PMID: 26438111
77. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125084s279lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf)
78. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125147s213lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf)
79. <https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food>
80. <https://investors.erasca.com/node/7891/pdf>
81. <https://ir.immuneering.com/news-releases/news-release-details/immuneering-granted-fda-fast-track-designation-imm-1-104>
82. Johnson et al. Treatment of NRAS-Mutant Melanoma. *Curr Treat Options Oncol.* 2015 Apr;16(4):15. doi: 10.1007/s11864-015-0330-z. PMID: 25796376
83. Dummer et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017 Apr;18(4):435-445. PMID: 28284557