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**Patient Name:** 임정숙
**Gender:** F
**Sample ID:** N25-239

**Primary Tumor Site:** Colon
**Collection Date:** 2023.12.12.

## Sample Cancer Type: Colon Cancer



### Report Highlights
4 Relevant Biomarkers
32 Therapies Available
107 Clinical Trials

## Relevant Colon Cancer Findings

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| BRAF | ***BRAF p.(V600E) c.1799T>A*** | 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 | ***25.85 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+]<br>**nivolumab** [1 / I, II+]<br>**pembrolizumab** [1, 2 / I, II+]<br>cemiplimab [I, II+]<br>dostarlimab [I, II+]<br>retifanlimab [I, II+]<br>tislelizumab [I, II+]<br>toripalimab [I, II+] | **dostarlimab** [2 / I, II+]<br>**ipilimumab + nivolumab** [2 / I, II+]<br>**pembrolizumab** [1, 2 / I, II+]<br>**dostarlimab + chemotherapy** [2]<br>cemiplimab [I, II+]<br>nivolumab [I, II+]<br>retifanlimab [I, II+]<br>tislelizumab [I, II+]<br>toripalimab [I, II+]<br>nivolumab + chemotherapy [I]<br>pembrolizumab + chemotherapy [I]<br>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 | | | |
| IA | *BRAF p.(V600E) c.1799T>A*<br>B-Raf proto-oncogene, serine/threonine kinase<br>Allele Frequency: 41.03%<br>Locus: chr7:140453136<br>Transcript: NM_004333.6 | **cetuximab + encorafenib** 1, 2 / I, II+<br>**cetuximab + encorafenib + chemotherapy** 1 / I, II+<br>**dabrafenib + trametinib** 1<br>encorafenib + panitumumab I, II+<br>encorafenib + panitumumab + chemotherapy I, II+<br>bevacizumab + chemotherapy I | **binimetinib + encorafenib** 1, 2 / I, II+<br>**cobimetinib + vemurafenib** 1, 2 / I, II+<br>**dabrafenib** 1, 2 / I, II+<br>**dabrafenib + trametinib** 1, 2 / I, II+<br>**vemurafenib** 1, 2 / I, II+<br>**atezolizumab + cobimetinib + vemurafenib** 1 / II+<br>**trametinib** 1, 2<br>cetuximab + encorafenib I, II+<br>cetuximab + encorafenib + chemotherapy I, II+<br>encorafenib I, II+<br>encorafenib + panitumumab I, II+<br>encorafenib + panitumumab + chemotherapy I, II+<br>ipilimumab + nivolumab I, II+<br>anti-PD-1 II+<br>dabrafenib + pembrolizumab + trametinib II+<br>ipilimumab II+<br>nivolumab II+<br>nivolumab + relatlimab II+<br>pembrolizumab II+<br>dabrafenib + MEK inhibitor selumetinib | 30 |
| | **Prognostic significance:** ESMO: Poor | | | |
| IIC | *ATRX deletion*<br>ATRX, chromatin remodeler<br>Locus: chrX:76763769 | None* | None* | 1 |
| IIC | *RNF43 p.(T58Qfs*4) c.171delC*<br>ring finger protein 43<br>Allele Frequency: 40.54%<br>Locus: chr17:56492767<br>Transcript: NM_017763.6 | None* | None* | 1 |

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

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

| | |
|---|---|
| *Microsatellite instability-High* | **ATX-559** 1 |
| *BRAF p.(V600E) c.1799T>A* | **binimetinib + cetuximab + encorafenib** 1<br>**plixorafenib** 1 |

**Public data sources included in alerts: FDA**1, NCCN, **EMA**2, ESMO

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*CIC p.(N227S) c.680A>G, CIC p.(Q958*) c.2872C>T, CUL4B deletion, FBXW7 p.(R465C) c.1393C>T, FBXW7 p.(S668Vfs*39) c.2001delG, KMT2D p.(F3699Lfs*14) c.11093_11094insG, PBRM1 p.(N258Mfs*25) c.773delA, PIK3CA p.(E110del) c.328_330delGAA, PPP2R2A p.(G352*) c.1054G>T, RNASEH2B p.(N33Mfs*3) c.98delA, TP53 p.(R273C) c.817C>T, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-A p.(L180*) c.539T>A, HLA-B deletion, CSMD3 p.(L2969Yfs*7) c.8906delT, NQO1*

*p.(P187S) c.559C>T, ZRSR2 deletion, BCOR deletion, USP9X deletion, DDX3X deletion, KDM6A deletion, RBM10 deletion, KDM5C deletion, SMC1A deletion, AMER1 deletion, ZMYM3 deletion, STAG2 deletion, PHF6 deletion, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| BRAF | p.(V600E) | c.1799T>A | COSM476 | chr7:140453136 | 41.03% | NM_004333.6 | missense |
| RNF43 | p.(T58Qfs*4) | c.171delC | . | chr17:56492767 | 40.54% | NM_017763.6 | frameshift Deletion |
| CIC | p.(N227S) | c.680A>G | . | chr19:42791794 | 2.20% | NM_015125.5 | missense |
| CIC | p.(Q958*) | c.2872C>T | . | chr19:42795883 | 40.46% | NM_015125.5 | nonsense |
| FBXW7 | p.(R465C) | c.1393C>T | COSM22932 | chr4:153249385 | 38.64% | NM_033632.3 | missense |
| FBXW7 | p.(S668Vfs*39) | c.2001delG | . | chr4:153244155 | 30.18% | NM_033632.3 | frameshift Deletion |
| KMT2D | p.(F3699Lfs*14) | c.11093_11094insG | . | chr12:49427394 | 36.12% | NM_003482.4 | frameshift Insertion |
| PBRM1 | p.(N258Mfs*25) | c.773delA | . | chr3:52682399 | 43.94% | NM_018313.5 | frameshift Deletion |
| PIK3CA | p.(E110del) | c.328_330delGAA | COSM24710 | chr3:178916937 | 39.67% | NM_006218.4 | nonframeshift Deletion |
| PPP2R2A | p.(G352*) | c.1054G>T | . | chr8:26223912 | 27.77% | NM_002717.4 | nonsense |
| RNASEH2B | p.(N33Mfs*3) | c.98delA | . | chr13:51501571 | 44.37% | NM_024570.4 | frameshift Deletion |
| TP53 | p.(R273C) | c.817C>T | COSM10659 | chr17:7577121 | 40.00% | NM_000546.6 | missense |
| UGT1A1 | p.(G71R) | c.211G>A | COSM4415616 | chr2:234669144 | 50.98% | NM_000463.3 | missense |
| HLA-A | p.(L180*) | c.539T>A | . | chr6:29911240 | 73.68% | NM_001242758.1 | nonsense |
| CSMD3 | p.(L2969Yfs*7) | c.8906delT | . | chr8:113303806 | 28.98% | NM_198123.2 | frameshift Deletion |
| NQO1 | p.(P187S) | c.559C>T | . | chr16:69745145 | 99.55% | NM_000903.3 | missense |
| MYCL | p.(G212C) | c.634G>T | . | chr1:40363595 | 45.37% | NM_001033082.3 | missense |
| JAK1 | p.(G1097D) | c.3290G>A | . | chr1:65301158 | 36.86% | NM_002227.4 | missense |
| LMX1A | p.(A110T) | c.328G>A | . | chr1:165218813 | 40.49% | NM_001174069.1 | missense |
| CDC73 | p.(T422A) | c.1264A>G | . | chr1:193202232 | 25.91% | NM_024529.5 | missense |
| PARP1 | p.(A367V) | c.1100C>T | . | chr1:226570796 | 3.02% | NM_001618.4 | missense |
| OR2L8 | p.([E195G;G196C]) | c.584_586delAGGinsGGT | . | chr1:248112743 | 1.82% | NM_001001963.1 | missense, missense |
| CRIM1 | p.(C354R) | c.1060T>C | . | chr2:36704100 | 34.45% | NM_016441.3 | missense |
| EML4 | p.(L970R) | c.2909T>G | . | chr2:42557310 | 52.90% | NM_019063.5 | missense |
| SULT1C3 | p.(E37G) | c.110A>G | . | chr2:108863760 | 35.01% | NM_001008743.3 | missense |
| CYP27C1 | p.(A197T) | c.589G>A | . | chr2:127953041 | 39.08% | NM_001001665.3 | missense |
| PDCD1 | p.(S73G) | c.217A>G | . | chr2:242794992 | 37.40% | NM_005018.3 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| PBRM1 | p.(?) | c.2779+2T>C | . | chr3:52637535 | 37.97% | NM_018313.5 | unknown |
| FGFR4 | p.(G476D) | c.1427G>A | . | chr5:176520684 | 39.06% | NM_213647.3 | missense |
| CDKN1A | p.(P12T) | c.34C>A | . | chr6:36651912 | 38.78% | NM_078467.3 | missense |
| GUCA1B | p.(E52D) | c.156G>T | . | chr6:42162403 | 8.35% | NM_002098.6 | missense |
| HDAC9 | p.(R230W) | c.688C>T | . | chr7:18668996 | 44.91% | NM_178425.3 | missense |
| DNAH11 | p.(W250R) | c.748T>C | . | chr7:21599276 | 4.38% | NM_001277115.2 | missense |
| SUFU | p.(E441K) | c.1321G>A | . | chr10:104386956 | 2.94% | NM_016169.4 | missense |
| DNHD1 | p.(M760I) | c.2280G>A | . | chr11:6550284 | 41.41% | NM_144666.3 | missense |
| ETV6 | p.(I407del) | c.1218_1220delTAT | . | chr12:12038922 | 42.88% | NM_001987.5 | nonframeshift Deletion |
| KMT2D | p.(V275M) | c.823G>A | . | chr12:49447275 | 3.80% | NM_003482.4 | missense |
| LETMD1 | p.(?) | c.274+2T>C | . | chr12:51442970 | 5.56% | NM_001243689.2 | unknown |
| BRCA2 | p.(G1552C) | c.4654G>T | . | chr13:32913146 | 41.86% | NM_000059.4 | missense |
| SLX4 | p.(G1390S) | c.4168G>A | . | chr16:3639471 | 46.65% | NM_032444.4 | missense |
| SLX4 | p.(P188H) | c.563C>A | . | chr16:3656672 | 43.01% | NM_032444.4 | missense |
| CYLD | p.(N829D) | c.2485A>G | . | chr16:50828147 | 4.41% | NM_001042355.2 | missense |
| RAD51D | p.(S155A) | c.463T>G | . | chr17:33428324 | 42.43% | NM_133629.3 | missense |
| COLEC12 | p.(E603D) | c.1809G>T | . | chr18:334749 | 40.70% | NM_130386.3 | missense |
| SMAD4 | p.(R441S) | c.1321C>A | . | chr18:48603020 | 39.31% | NM_005359.6 | missense |
| SMARCA4 | p.(R528Q) | c.1583G>A | . | chr19:11105667 | 41.75% | NM_001128849.3 | missense |
| NOTCH3 | p.([Q505H;L506=]) | c.1515_1516delGCinsTT | . | chr19:15298782 | 51.55% | NM_000435.3 | missense, synonymous |
| NOTCH3 | p.(?) | c.119-1G>A | . | chr19:15308390 | 44.28% | NM_000435.3 | unknown |
| PPP2R1A | p.(R221W) | c.661C>T | . | chr19:52716217 | 40.35% | NM_014225.6 | missense |
| RBM10 | p.(L198P) | c.593T>C | . | chrX:47030623 | 67.91% | NM_001204468.1 | missense |

## Copy Number Variations

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| ATRX | chrX:76763769 | 0.93 | 0.61 |
| CUL4B | chrX:119660593 | 1.11 | 0.67 |
| HLA-A | chr6:29910229 | 0.72 | 0.52 |
| HLA-B | chr6:31322252 | 0.96 | 0.61 |
| ZRSR2 | chrX:15808582 | 1.01 | 0.63 |
| BCOR | chrX:39911340 | 1.03 | 0.64 |
| USP9X | chrX:40982869 | 1 | 0.63 |

# Variant Details (continued)

## Copy Number Variations (continued)

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| DDX3X | chrX:41193501 | 0.84 | 0.57 |
| KDM6A | chrX:44732715 | 1.07 | 0.65 |
| RBM10 | chrX:47006798 | 1.04 | 0.65 |
| KDM5C | chrX:53221892 | 1.07 | 0.66 |
| SMC1A | chrX:53406966 | 0.97 | 0.62 |
| AMER1 | chrX:63409727 | 0.97 | 0.62 |
| ZMYM3 | chrX:70460753 | 0.99 | 0.63 |
| STAG2 | chrX:123156472 | 1.04 | 0.65 |
| PHF6 | chrX:133511628 | 0.93 | 0.6 |
| ARAF | chrX:47422311 | 1 | 0.63 |
| AR | chrX:66766015 | 1.08 | 0.66 |

# 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[54]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[55,56]. MSI is closely tied to the status of the mismatch repair (MMR) genes[57]. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[57]. 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[58]. 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)[58]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[59,60,61,62,63]. 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[56]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[55,56,60,64].

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[55,56,65,66]. 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[65,66]. MSI-H is rare in pediatric solid tumors and is primarily observed in high grade gliomas, including astrocytoma and oligodendroglioma[67,68].

Potential relevance: Anti-PD-1 immune checkpoint inhibitor pembrolizumab[69] (2014) is approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[69] 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[69]. Dostarlimab[70] (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[61,71,72,73,74,75,76,77,78,79]. Nivolumab[80] (2015) is approved as a single agent or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[81] (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[61,82,83]. 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[83]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune

## Biomarker Descriptions (continued)

checkpoint inhibitors, compared to those with MSI-H tumors[84,85]. However, combining checkpoint blockade with chemotherapy or targeted therapies has demonstrated responses in MSS or pMMR cancers[84,85].

**BRAF p.(V600E) c.1799T>A**

*B-Raf proto-oncogene, serine/threonine kinase*

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1(CRAF)[98]. BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[99,100]. BRAF mutations are categorized into three distinct functional classes, namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway[101]. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[101]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[101,102,103].

Alterations and prevalence: Somatic mutations in BRAF are observed in 59% of thyroid carcinoma, 53% of skin cutaneous melanoma, 12% of colorectal adenocarcinoma, 8% of lung adenocarcinoma, 5% of uterine corpus endometrial carcinoma, and 2-3% of bladder urothelial carcinoma, lung squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, diffuse large B-cell lymphoma, glioblastoma multiforme, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[102,104]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[102]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[102]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[105,106,107]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11, as well as additional codons flanking V600 in the activation loop[104]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[5,6]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[108,109,110,111,112]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[103,108,110]. Alterations in BRAF are rare in pediatric cancers, with the most predominant being the V600E mutation and the BRAF::KIAA1549 fusion, both of which are observed in low-grade gliomas[113]. Somatic mutations are observed in 6% of glioma and less than 1% of bone cancer (2 in 327 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[5,6]. Amplification of BRAF is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[5,6].

Potential relevance: Vemurafenib[114] (2011) is the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, and it is also approved for BRAF V600E-positive Erdheim-Chester Disease (2017). BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[102]. BRAF kinase inhibitors including dabrafenib[115] (2013) and encorafenib[116] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[116] is approved in combination with cetuximab[117] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[102]. The MEK inhibitors, trametinib[118] (2013) and binimetinib[119] (2018), were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC[120]. The combinations of dabrafenib/trametinib[118](2015) and vemurafenib/cobimetinib[121] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017), children with low-grade gliomas, and children and adults with solid tumors (2022) harboring a BRAF V600E mutation[115]. The PD-L1 antibody, atezolizumab[122], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The FDA has granted fast track designation (2023) to ABM-1310[123] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[124] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[125] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[126], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. The FDA also granted fast track designation (2023) to the BRAF inhibitor, plixorafenib (PLX-8394)[127], for BRAF Class I (V600) and Class II (including fusions) altered cancer patients who have already undergone previous treatments. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[128]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification, alternative splice transcripts, as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[129,130,131,132,133,134,135]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[112].

## Biomarker Descriptions (continued)

**ATRX deletion**

*ATRX, chromatin remodeler*

Background: The ATRX gene encodes the ATRX chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins[1]. The SWI/SNF proteins are a group of DNA translocases that use ATP hydrolysis to remodel chromatin structure and maintain genomic integrity by controlling transcriptional regulation, DNA repair, and chromosome stability through the regulation of telomere length[198,199,200,201]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[202,203,204].

Alterations and prevalence: Somatic mutations of ATRX are observed in 38% of brain lower grade glioma, 15% of uterine corpus endometrial carcinoma, 14% of sarcoma, 9% of glioblastoma multiforme and skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of lung adenocarcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma, 5% of bladder urothelial carcinoma and lung squamous cell carcinoma, 4% of adrenocortical carcinoma, head and neck squamous cell carcinoma and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, pheochromocytoma and paraganglioma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma and kidney chromophobe[5,6]. Biallelic deletion of ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[5,6]. Although alterations of ATRX in pediatric populations are rare, somatic mutations are observed in 6% of gliomas, 4% of bone cancer, 3% of soft tissue sarcoma, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (3 in 332 cases), and leukemia (2 in 354 cases)[6]. Biallelic deletion of ATRX is observed in 1% of peripheral nervous system tumors (1 in 91 cases) in and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[205,206]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[207,208].

**RNF43 p.(T58Qfs*4) c.171delC**

*ring finger protein 43*

Background: The RNF43 gene encodes the ring finger protein 43[1]. RNF43 is a transmembrane E3 ubiquitin ligase and a negative regulator of the Wnt signaling pathway[222,223]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[222]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[222,223].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[5,6]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[222,224,225].

Potential relevance: Currently, no therapies are approved for RNF43 aberrations.

**CIC p.(N227S) c.680A>G, CIC p.(Q958*) c.2872C>T**

*capicua transcriptional repressor*

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,169]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,169]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[169]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[169].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[5,6]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[169,170].

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[171,172].

## Biomarker Descriptions (continued)

**CUL4B deletion**

*cullin 4B*

Background: The CUL4B gene encodes cullin 4B, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4a, CUL5, CUL7, and Parc[1,2]. CUL4B belongs to the CUL4 subfamily which also includes CUL4A[3]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[3,4]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. CUL4B is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[4]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4B in oncogenesis[3,4].

Alterations and prevalence: Somatic mutations in CUL4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 2% of bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, uterine carcinosarcoma, brain lower grade glioma, and lung squamous cell carcinoma[5,6]. Amplification of CUL4B is observed in 2% of diffuse large B-cell lymphoma[5,6]. Biallelic loss of CUL4B is observed in 1% sarcoma and testicular germ cell tumors[5,6].

Potential relevance: Currently, no therapies are approved for CUL4B aberrations.

**FBXW7 p.(R465C) c.1393C>T, FBXW7 p.(S668Vfs*39) c.2001delG**

*F-box and WD repeat domain containing 7*

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[136]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[136,137,138,139,140,141,142].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[5,6,143,144,145].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[146], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[143]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[142].

**KMT2D p.(F3699Lfs*14) c.11093_11094insG**

*lysine methyltransferase 2D*

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[34]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[34]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[34].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[5,6].

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

## Biomarker Descriptions (continued)

**PBRM1 p.(N258Mfs*25) c.773delA**

*polybromo 1*

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[25]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[25,26]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[25,27]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[28,29].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[5,6]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

**PIK3CA p.(E110del) c.328_330delGAA**

*phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[147]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[148,149]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[148]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[150,151]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[150,151,152,153]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[154,155,156].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[5,6]. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[157,158]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[159,160,161]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[5,6].

Potential relevance: The PI3K inhibitor, alpelisib[162], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[163]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[163]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[164]. The FDA also approved the kinase inhibitor, capivasertib (2023)[165] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[166], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[167,168].

**PPP2R2A p.(G352*) c.1054G>T**

*protein phosphatase 2 regulatory subunit Balpha*

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[10,11]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-

## Biomarker Descriptions (continued)

apoptotic activity through negative regulation of the PI3K/AKT pathway[12]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[10].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[10,11,13,14]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[5].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[10]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[16].

**RNASEH2B p.(N33Mfs*3) c.98delA**

*ribonuclease H2 subunit B*

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[215,216]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[215]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[215].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[5,6]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[5,6].

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

**TP53 p.(R273C) c.817C>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[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[226]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[227]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[228,229].

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%)[5,6,230,231,232,233]. 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[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[234,235,236,237]. Alterations in TP53 are also observed in pediatric cancers[5,6]. 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 )[5,6]. 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)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[238] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[239], (2019) and breakthrough designation[240] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[241,242]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[207]. 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)[178,186,187,243,244,245]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[246]. 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

## Biomarker Descriptions (continued)

mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[247].

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

*UDP glucuronosyltransferase family 1 member A1*

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,41]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[41,42]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[43]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[43,44,45,46]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[47].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[5,6].

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

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

*major histocompatibility complex, class I, A*

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[48]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[49]. 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[50,51,52]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[53].

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[5,6]. Biallelic loss of HLA-A is observed in 4% of DLBCL[5,6].

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[48]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[49]. 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[50,51,52]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[53].

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[5,6]. Biallelic loss of HLA-B is observed in 5% of DLBCL[5,6].

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

## Biomarker Descriptions (continued)

**CSMD3 p.(L2969Yfs*7) c.8906delT**

*CUB and Sushi multiple domains 3*

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,7]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins[7,8]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[7,8]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[7,9].

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[5,6]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

**ZRSR2 deletion**

*zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2*

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site[217]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[217,218]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[217,219].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[6,178].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[178,186,187].

**BCOR deletion**

*BCL6 corepressor*

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) co-repressor protein, which potentiates transcriptional repression by BCL6[173,174]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism for BCOR-mediated transcriptional repression independent of BCL6[174]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[175,176,177].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[5,178,179,180]. Higher mutational frequencies are reported in some solid tumors, including up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma[5,6]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[181,182,183]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[184,185]. Alterations in BCOR are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 13% of soft tissue sarcoma, 4% of glioma, 3% of retinoblastoma, 2% of bone cancer, 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), and Wilms tumor (2 in 710 cases)[5,6]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[181].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR::CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[171,172]. Additionally, translocation t(x;22)(p11;q13)

## Biomarker Descriptions (continued)

resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[171]. Somatic mutation in BCOR is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR) and is associated with poor prognosis in AML and MDS[178,179,186,187,188]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse-free survival (RFS) compared to those without BCOR abnormalities (OS = 13.6% vs. 55%; RFS = 14.3% vs. 44.5%)[180]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[189,190].

**USP9X deletion**

*ubiquitin specific peptidase 9 X-linked*

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-lined protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[17]. DUBs are responsible for protein deubiquitination, thereby counter-regulating post-transcriptional ubiquitin modification of proteins within the cell[17,18]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[18]. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its subtrates[18]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[18].

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma[5,6]. Biallelic deletions are observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

**DDX3X deletion**

*DEAD-box helicase 3, X-linked*

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II[1,86]. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)[86,87,88,89]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[86]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[90,91,92,93,94,95,96,97]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[90].

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma[5,6]. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

**KDM6A deletion**

*lysine demethylase 6A*

Background: The KDM6A gene encodes the lysine demethylase 6A protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[220]. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression[196]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[195,220]. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation[220]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[220]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[220,221].

Alterations and prevalence: Somatic mutations in KDM6A are observed in 26% of bladder urothelial carcinoma, 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma, and head and neck squamous

## Biomarker Descriptions (continued)

cell carcinoma[5,6]. Biallelic loss of KDM6A is observed in 8% of esophageal adenocarcinoma, 4% of lung squamous cell carcinoma, 3% of head and neck squamous cell carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors[221].

**RBM10 deletion**

*RNA binding motif protein 10*

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,191]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[191,192]. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression[191]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[193,194].

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6]. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for RBM10 aberrations.

**KDM5C deletion**

*lysine demethylase 5C*

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,195]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[196]. KDM5C removes methylation of di- and trimethylated histone H3 lysine 4 (H3K4) and is involved in the repression of transcription in response to DNA damage[195,196]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[197].

Alterations and prevalence: Somatic mutations in KDM5C are observed in 9% of uterine corpus endometrial carcinoma, 5% of kidney renal clear cell carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, 4% of lung adenocarcinoma and uterine carcinosarcoma[5,6]. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM5C aberrations.

**SMC1A deletion**

*structural maintenance of chromosomes 1A*

Background: SMC1A encodes the structural maintenance of chromosomes 1A and belongs to structural maintenance of chromosomes (SMCs) family, which consists of SMC1A, SMC1B, SMC2, SMC3, SMC4, SMC5, and SMC6[1,30,31]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[30,32]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[30]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[31,33].

Alterations and prevalence: Somatic mutations in SMC1A are observed in 11% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma and acute myeloid leukemia, 4% of colorectal adenocarcinoma and bladder urothelial carcinoma, 3% cervical squamous cell carcinoma and glioblastoma multiforme, 2% diffuse large B-Cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma and lung adenocarcinoma[5,6]. Amplification of SMC1A is found in 4% of diffuse large B-Cell lymphoma, 3% of sarcoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of SMC1A is found in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

## Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for SMC1A aberrations.

**AMER1 deletion**

*APC membrane recruitment protein 1*

Background: The AMER1 gene encodes APC membrane recruitment protein 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,35]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[36,37]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[37]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[38]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[35].

Alterations and prevalence: Somatic mutations of AMER1 are observed in 13% of colorectal adenocarcinoma,10% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 4% of stomach adenocarcinoma, and uterine carcinosarcoma, 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and breast invasive carcinoma[5,6]. Biallelic deletion of AMER1 is observed in 2% of esophageal adenocarcinoma, diffuse large b-cell lymphoma, uterine carcinosarcoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma, and 1% of stomach adenocarcinoma, sarcoma, liver hepatocellular carcinoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for AMER1 aberrations.

**ZMYM3 deletion**

*zinc finger MYM-type containing 3*

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[39].

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[40]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for ZMYM3 aberrations.

**STAG2 deletion**

*stromal antigen 2*

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[209,210]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[211,212]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[211,213].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[178]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[6]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[6,178].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[178,186,187]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[214].

## Biomarker Descriptions (continued)

**PHF6 deletion**

*PHD finger protein 6*

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[19,20].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[19,21,22,23]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[21,23]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[21]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[19,21].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[24].

# 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

## BRAF p.(V600E) c.1799T>A

### binimetinib + cetuximab + encorafenib

**Cancer type:** Colorectal Cancer **Variant class:** BRAF V600E mutation

**Supporting Statement:**
The FDA has granted Breakthrough Therapy designation to the MEK inhibitor, binimetinib, in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer.

**Reference:**

https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791

## BRAF p.(V600E) c.1799T>A (continued)

### plixorafenib

**Cancer type:** Solid Tumor **Variant class:** BRAF V600 mutation

**Supporting Statement:**
The FDA has granted Fast Track designation to a novel small molecule inhibitor, plixorafenib (PLX-8394), for the treatment of patients with cancers harboring BRAF Class 1 (V600) and Class 2 (including fusions) alterations who have exhausted prior therapies.

**Reference:**

https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/

### ABM-1310

**Cancer type:** Glioblastoma IDH-wildtype (Grade 4) **Variant class:** BRAF V600E mutation

**Supporting Statement:**
The FDA has granted Fast Track designation to ABM-1310 for the treatment of glioblastoma (GBM) patients with BRAF V600E mutation.

**Reference:**

https://www.prnewswire.com/news-releases/abm-therapeutics-abm-1310-granted-fast-track-designation-by-the-fda-following-orphan-drug-designation-301937168.html

### Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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



## Microsatellite instability-High

### pembrolizumab

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

**Summary:**

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

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

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

# Genes Assayed

## Genes Assayed for the Detection of DNA Sequence Variants

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

## Genes Assayed for the Detection of Copy Number Variations

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

* 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* |
|---|---|---|---|---|---|
| catequentinib, penpulimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| catequentinib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| cemiplimab, fianlimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| dostarlimab, chemoradiation therapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| durvalumab, tremelimumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| envafolimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| KN046, regorafenib, apatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| 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) |

* 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* |
|---|---|---|---|---|---|
| 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) |
| 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) |

* 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

### BRAF p.(V600E) c.1799T>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| dabrafenib + trametinib | ◑ | ○ | ○ | ○ | ✖ |
| cetuximab + encorafenib | ● | ◑ | ● | ● | ✖ |
| cetuximab + encorafenib + FOLFOX | ● | ◑ | ✖ | ✖ | ✖ |
| cobimetinib + vemurafenib | ○ | ○ | ○ | ○ | ● (II/III) |
| binimetinib + encorafenib | ○ | ○ | ○ | ○ | ✖ |
| dabrafenib | ○ | ○ | ○ | ✖ | ● (II) |
| vemurafenib | ○ | ○ | ○ | ✖ | ✖ |
| atezolizumab + cobimetinib + vemurafenib | ○ | ○ | ✖ | ✖ | ✖ |
| trametinib | ○ | ✖ | ○ | ✖ | ✖ |
| encorafenib + panitumumab | ✖ | ◑ | ✖ | ✖ | ✖ |
| encorafenib + panitumumab + FOLFOX | ✖ | ◑ | ✖ | ✖ | ✖ |
| encorafenib | ✖ | ○ | ✖ | ○ | ✖ |
| dabrafenib + pembrolizumab + trametinib | ✖ | ○ | ✖ | ✖ | ✖ |
| selumetinib | ✖ | ○ | ✖ | ✖ | ✖ |
| bevacizumab + CAPOX | ✖ | ✖ | ✖ | ● | ✖ |
| bevacizumab + FOLFOX | ✖ | ✖ | ✖ | ● | ✖ |
| bevacizumab + FOLFOXIRI | ✖ | ✖ | ✖ | ● | ✖ |
| nivolumab | ✖ | ✖ | ✖ | ○ | ● (III) |
| anti-PD-1 | ✖ | ✖ | ✖ | ○ | ✖ |
| dabrafenib + MEK inhibitor | ✖ | ✖ | ✖ | ○ | ✖ |
| ipilimumab | ✖ | ✖ | ✖ | ○ | ✖ |
| ipilimumab + nivolumab | ✖ | ✖ | ✖ | ○ | ✖ |
| nivolumab + relatlimab | ✖ | ✖ | ✖ | ○ | ✖ |
| pembrolizumab | ✖ | ✖ | ✖ | ○ | ✖ |
| cetuximab, binimetinib, encorafenib | ✖ | ✖ | ✖ | ✖ | ● (II/III) |
| bevacizumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| bevacizumab, chemotherapy, leucovorin | ✖ | ✖ | ✖ | ✖ | ● (II) |
| cetuximab, encorafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| cetuximab, panitumumab, encorafenib, antimalarial | ✖ | ✖ | ✖ | ✖ | ● (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

### BRAF p.(V600E) c.1799T>A (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| cetuximab, vemurafenib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| encorafenib, cetuximab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| tunlametinib, vemurafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| vemurafenib, cetuximab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| vemurafenib, cetuximab, chemotherapy, bevacizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| chemotherapy, KSQ-004, aldesleukin | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| donafenib, trametinib, cetuximab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| RX208, serplulimab | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| RX208, trametinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| CGX-1321, encorafenib, cetuximab | ✖ | ✖ | ✖ | ✖ | ● (I) |
| exarafenib, binimetinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| HSK42360 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| IK-595 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| JSI-1187 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| PF-07799933, cetuximab, binimetinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| RMC-6236 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| RO-7276389, cobimetinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| RX208 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ulixertinib, cetuximab, encorafenib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ZEN-3694, cetuximab, encorafenib | ✖ | ✖ | ✖ | ✖ | ● (I) |

### ATRX deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

### RNF43 p.(T58Qfs*4) c.171delC

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| CGX-1321, encorafenib, cetuximab | ✖ | ✖ | ✖ | ✖ | ● (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 | ***5.31%*** |
| BRCA2 | ***SNV, G1552C, AF:0.42*** |

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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