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Patient Name: 유진홍
Gender: M
Sample ID: N25-189

Primary Tumor Site: lung
Collection Date: 2025.08.21

Sample Cancer Type: Lung Cancer

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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	***BRAF p.(V600E) c.1799T>A***	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	***4.75 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 18.19% Locus: chr7:140453136 Transcript: NM_004333.6	**binimetinib + encorafenib** [1, 2 / I, II+] **dabrafenib + trametinib** [1, 2 / I, II+] dabrafenib [I] vemurafenib [I]	**binimetinib + encorafenib** [1, 2 / I, II+] **cetuximab + encorafenib** [1, 2 / I, II+] **cetuximab + encorafenib + chemotherapy** [1 / I, II+] **cobimetinib + vemurafenib** [1, 2 / I, II+] **dabrafenib** [1, 2 / I, II+] **dabrafenib + trametinib** [1, 2 / I, II+] **vemurafenib** [1, 2 / I, II+] **atezolizumab + cobimetinib + vemurafenib** [1 / II+] **trametinib** [1, 2] encorafenib [I, II+] encorafenib + panitumumab [I, II+] encorafenib + panitumumab + chemotherapy [I, II+] ipilimumab + nivolumab [I, II+]	24

*** 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
			bevacizumab + chemotherapy [I] anti-PD-1 [II+] dabrafenib + pembrolizumab + trametinib [II+] ipilimumab [II+] nivolumab [II+] nivolumab + relatlimab [II+] pembrolizumab [II+] dabrafenib + MEK inhibitor selumetinib	

*** 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

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

CBL p.(C396Y) c.1187G>A, FGFR2 p.(G271R) c.811G>A, KEAP1 p.(D422N) c.1264G>A, Microsatellite stable, SETD2 p.(F2505) c.7514_7515delTT, TP53 p.(Y163C) c.488A>G, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-B deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	18.19%	NM_004333.6	missense
CBL	p.(C396Y)	c.1187G>A	COSM34067	chr11:119148967	2.77%	NM_005188.4	missense
FGFR2	p.(G271R)	c.811G>A	.	chr10:123279621	9.32%	NM_000141.5	missense
KEAP1	p.(D422N)	c.1264G>A	COSM710198	chr19:10602314	10.37%	NM_203500.2	missense
SETD2	p.(F2505*)	c.7514_7515delTT	.	chr3:47059145	13.04%	NM_014159.7	nonsense
TP53	p.(Y163C)	c.488A>G	COSM10808	chr17:7578442	11.36%	NM_000546.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	47.90%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	49.70%	NM_000903.3	missense
EGFR	p.(K293R)	c.878A>G	.	chr7:55221834	12.07%	NM_005228.5	missense
PALB2	p.(E956K)	c.2866G>A	.	chr16:23634420	13.19%	NM_024675.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-A	chr6:29910229	0.47	0.54
HLA-B	chr6:31322252	0.82	0.64

Biomarker Descriptions

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)[62]. 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[63,64]. 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[65]. 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[65]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[65,66,67].

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[9,18]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[66,68]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[66]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[66]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[69,70,71]. 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[68]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[9,18]. 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[72,73,74,75,76]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[67,72,74]. 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[77]. 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)[9,18]. 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)[9,18].

Potential relevance: Vemurafenib[78] (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[66]. BRAF kinase inhibitors including dabrafenib[79] (2013) and encorafenib[80] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[80] is approved in combination with cetuximab[81] (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[66]. The MEK inhibitors, trametinib[82] (2013) and binimetinib[83] (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[84]. The combinations of dabrafenib/trametinib[82](2015) and vemurafenib/cobimetinib[85] (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[79]. The PD-L1 antibody, atezolizumab[86], 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[87] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[88] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[89] 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[90], 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)[91], 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[92]. 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)[93,94,95,96,97,98,99]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[76].

CBL p.(C396Y) c.1187G>A

Cbl proto-oncogene

Background: The CBL gene encodes the casitas B-lineage lymphoma (CBL) ubiquitin ligase, a member of the ubiquitin ligase (E3) protein family that also includes CBL-b and CBL-c[49]. CBL proteins are characterized by their highly conserved N-terminal tyrosine

Biomarker Descriptions (continued)

kinase binding (TKB) domain and RING finger (RF) catalytic domain which are directly involved in the regulation of receptor tyrosine kinase (RTK) signaling[49,50]. Upon recognition of an activated RTK via its TKB domain, CBL mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme (E2) via its RF domain, consequently targeting the RTK for proteasome degradation. CBL can also function as an adaptor protein via recruitment of signaling molecules to active RTKs[50]. CBL is the target of genetic aberrations, including missense mutations and translocations, which can lead to oncogenic transformation in hematological malignancies as well as solid tumors[50,51,52,53]. Mutations in CBL often result in a loss of E3 ligase activity, thereby preventing proteasome-mediated RTK degradation, which supports the role of CBL as a tumor suppressor gene[51]. However, CBL mutants often maintain their adapter function, contributing to their transforming potential and suggesting a simultaneous oncogenic role for CBL in cancer[50]. Hereditary mutations in CBL lead to constitutive activation of RAS and MAPK pathways resulting in genetic disorders known as RASopathies which can lead to increased cancer risk[43].

Alterations and prevalence: Genetic alterations in CBL were first recognized in acute myeloid leukemia (AML) as a result of an interstitial deletion leading to MLL::CBL fusion[54,55]. However, fusions involving CBL are relatively rare. Aberrations in CBL most often involve missense mutations which commonly cluster in the linker region or RF domain corresponding to exons 8 and 9[50,51]. Such mutations lead to disruption of E3 ligase activity and have been reported in systemic mastocytosis (SM), 1-3% of de novo AML, 10% of secondary AML, 8% of atypical AML, and 10-15% of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)[9,50,56,57,58,59,60]. Mutations in CBL have also been reported in 1-6% of melanomas, lung, stomach, colorectal, esophageal, and uterine cancers[9,53].

Potential relevance: Mutations in CBL confer adverse prognosis in SM and have been shown to be independently predictive of inferior survival[57,61].

FGFR2 p.(G271R) c.811G>A

fibroblast growth factor receptor 2

Background: The FGFR2 gene encodes fibroblast growth receptor 2, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR1, 3, and 4[11]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[11]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[100,101,102].

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[103]. Somatic mutations in FGFR2 are observed in 15% of uterine corpus endometrial carcinomas, 10% of skin cutaneous melanoma, 6% of cholangiocarcinoma, 4% of stomach adenocarcinoma, 3% of colorectal adenocarcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[9,18]. In endometrial cancers, missense mutations are the most prevalent alterations in FGFR2[104]. These mutations are predominantly activating, most often involve substitutions at S252 and P253, and confer sensitivity to pan-FGFR2 inhibitors[104,105]. FGFR2 amplification occurs in up to 4% of stomach adenocarcinoma, and 2% of ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and uterine corpus endometrial carcinoma[9,18]. FGFR2 fusions have also been reported in up to 14% of cholangiocarcinoma and confer sensitivity to select FGFR inhibitors[9,106,107]. Aberrations in FGFR2 are rare in pediatric cancers[9,18]. Somatic mutations in FGFR2 occur in 2% of T-lymphoblastic leukemia/lymphoma and FGFR2 is amplified in 2% of bone cancer[9,18].

Potential relevance: Several pan-FGFR inhibitors have been approved for FGFR2 aberrations in cancer. Futibatinib[108] (2022) is approved for FGFR2 fusion-positive locally advanced or metastatic intrahepatic cholangiocarcinoma and has been granted breakthrough designation[109] (2022) for FGFR2-fusion positive cholangiocarcinoma. Erdafitinib[110] (2019) is approved for the treatment of locally advanced or metastatic urothelial cancer with FGFR2 fusions, including FGFR2::BICC1 and FGFR2::CASP7. Pemigatinib[111] (2020) is approved for previously treated, advanced, or unresectable cholangiocarcinoma harboring FGFR2 fusions. The FDA has granted fast track designation to the pan-FGFR inhibitor, KIN-3248[112](2023), for unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusions or other alterations after receiving at least one prior systemic therapy. The FDA has also granted fast track designation to the FGFR2 inhibitor, 3HP-2827[113] (2024), for the treatment of patients with cholangiocarcinoma harboring FGFR2 mutations. The FDA has granted breakthrough designation to the FGFR2 inhibitor, lirafugratinib[114] (2024), for the treatment of FGFR2-driven cholangiocarcinoma and other FGFR2-altered solid tumors. The FDA also granted fast track designation to the small molecule inhibitor, Debio 1347[115] (2018), for solid tumors harboring FGFR1, FGFR2, or FGFR3 aberrations. The FDA has granted breakthrough designation to bemarituzumab[116] (2021), in combination with modified FOLFOX6 (fluoropyrimidine, leucovorin, and oxaliplatin), for treating FGFR2b-overexpressing, HER2-negative metastatic and locally advanced gastric and gastroesophageal adenocarcinoma. Additional FGFR inhibitors are under clinical evaluation for FGFR2 aberrations[117,118]. In a phase II study of patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma, the pan-kinase inhibitor derazantinib, demonstrated an overall response rate (ORR) of 20.7% with progression-free survival (PFS) of 5.7 months[117]. Likewise, results of a phase II trial testing the pan-FGFR inhibitor, infigratinib

Biomarker Descriptions (continued)

(BGJ398) demonstrated an ORR of 14.8% (18.8% FGFR2 fusions only), disease control rate (DCR) of 75.4% (83.3% FGFR2 fusions only), and a median PFS of 5.8 months[118].

KEAP1 p.(D422N) c.1264G>A

kelch like ECH associated protein 1

Background: The KEAP1 gene encodes the kelch like ECH associated protein 1, a tumor suppressor and a member of the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex[11,19]. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2[20]. Aberrations in KEAP1 can result in loss of function leading to accumulation of NFE2L2, thereby altering the transcription genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation[20,21,22].

Alterations and prevalence: Somatic mutations in KEAP1 are observed in 18% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, and 4% of head and neck squamous cell carcinoma[9,18].

Potential relevance: Currently, no therapies are approved for KEAP1 aberrations.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[119]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[120,121]. 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[122]. 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[123]. 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)[123]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[124,125,126,127,128]. 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[121]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[120,121,125,129].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[120,121,130,131]. 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[130,131].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[132] (2014) and nivolumab[133] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[132] 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[132]. Dostarlimab[134] (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[126,135]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[136] (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[126,137,138]. 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[138]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[139,140]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[139,140].

SETD2 p.(F2505*) c.7514_7515delTT

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[1,2]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[3]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[4,5]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[2]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR

Biomarker Descriptions (continued)

deficiency (dMMR) and consequent microsatellite instability (MSI)[6]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[2,7].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[7,8,9]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[1,9]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[1]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[1].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[10].

TP53 p.(Y163C) c.488A>G

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[11]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[23]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[24]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[25,26].

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%)[9,18,27,28,29,30]. 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[9,18]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[31,32,33,34]. Alterations in TP53 are also observed in pediatric cancers[9,18]. 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)[9,18]. 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)[9,18].

Potential relevance: The small molecule p53 reactivator, PC14586[35] (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[36], (2019) and breakthrough designation[37] (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[38,39]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[40]. 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)[41,42,43,44,45,46]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[47]. 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[48].

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[11,141]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[141,142]. 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[143]. 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[143,144,145,146]. 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[147].

Biomarker Descriptions (continued)

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[9,18].

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[11]. 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[12]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[13]. 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[14,15,16]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[17].

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[9,18]. Biallelic loss of HLA-A is observed in 4% of DLBCL[9,18].

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[11]. 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[12]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[13]. 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[14,15,16]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[17].

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[9,18]. Biallelic loss of HLA-B is observed in 5% of DLBCL[9,18].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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

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

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, 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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + trametinib	◑	◑	◑	◑	● (II)
binimetinib + encorafenib	◑	◑	◑	○	✖
dabrafenib	○	◑	○	✖	● (II)
vemurafenib	○	◑	○	✖	✖
cobimetinib + vemurafenib	○	○	○	○	● (II/III)
cetuximab + encorafenib	○	○	○	○	✖
atezolizumab + cobimetinib + vemurafenib	○	○	✖	✖	✖
cetuximab + encorafenib + FOLFOX	○	○	✖	✖	✖
trametinib	○	✖	○	✖	✖
encorafenib	✖	○	✖	○	✖
dabrafenib + pembrolizumab + trametinib	✖	○	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
encorafenib + panitumumab + FOLFOX	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
anti-PD-1	✖	✖	✖	○	✖
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
nivolumab	✖	✖	✖	○	✖
nivolumab + relatlimab	✖	✖	✖	○	✖
pembrolizumab	✖	✖	✖	○	✖
sacituzumab tirumotecan	✖	✖	✖	✖	● (III)
trametinib, dabrafenib	✖	✖	✖	✖	● (III)
dabrafenib, trametinib	✖	✖	✖	✖	● (II)
RX208	✖	✖	✖	✖	● (II)
sacituzumab govitecan	✖	✖	✖	✖	● (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*
toripalimab, chemotherapy	✖	✖	✖	✖	● (II)
tunlametinib, vemurafenib	✖	✖	✖	✖	● (II)
benmelstobart, catequentinib	✖	✖	✖	✖	● (I/II)
RX208, serplulimab	✖	✖	✖	✖	● (I/II)
RX208, trametinib	✖	✖	✖	✖	● (I/II)
exarafenib, binimetinib	✖	✖	✖	✖	● (I)
HSK42360	✖	✖	✖	✖	● (I)
IBI-363, IBI-325, lenvatinib	✖	✖	✖	✖	● (I)
IK-595	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
JSKN-016	✖	✖	✖	✖	● (I)
PF-07799933, cetuximab, binimetinib	✖	✖	✖	✖	● (I)
RO-7276389, cobimetinib	✖	✖	✖	✖	● (I)
ZEN-3694, binimetinib	✖	✖	✖	✖	● (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%***
PALB2	***SNV, E956K, AF:0.13***

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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