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

Patient Name: 이명순B
Gender: M
Sample ID: N25-61

Primary Tumor Site: Colon
Collection Date: 2025.06.04

Sample Cancer Type: Colon Cancer

Report Highlights

5 Relevant Biomarkers
3 Therapies Available
18 Clinical Trials

Relevant Colon Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK2	None detected
ERBB2	***ERBB2 p.(R678Q) c.2033G>A***	NTRK3	None detected
KRAS	None detected	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***46.73 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
IIC	*ERBB2 p.(R678Q) c.2033G>A* erb-b2 receptor tyrosine kinase 2 Allele Frequency: 29.90% Locus: chr17:37879658 Transcript: NM_004448.4	None*	**trastuzumab deruxtecan** [1, 2] neratinib [II+]	11
IIC	*PIK3CA p.(E453K) c.1357G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 23.79% Locus: chr3:178928079 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1 / I]	4

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*MSH2 deletion* mutS homolog 2 Locus: chr2:47630288	None*	None*	1
IIC	*RAD51 p.(R194*) c.580C>T* RAD51 recombinase Allele Frequency: 25.45% Locus: chr15:41020955 Transcript: NM_133487.4	None*	None*	1
IIC	*TP53 p.(R273H) c.818G>A* tumor protein p53 Allele Frequency: 28.55% Locus: chr17:7577120 Transcript: NM_000546.6	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC p.(R1687) c.5059C>T, CIC p.(R1515H) c.4544G>A, ERBB3 p.(A232V) c.695C>T, FAT1 p.(T2369Rfs*2) c.7105delA, GNAS p.(R201H) c.602G>A, KEAP1 p.(R498*) c.1492C>T, PIK3R1 p.(R358*) c.1072C>T, PPP2R2A p.(R153*) c.457C>T, SETD2 p.(R1407Gfs*5) c.4219delA, SLX4 p.(D1424*) c.4269_4270insT, TP53 p.(G245S) c.733G>A, EPHA2 p.(P460Rfs*33) c.1379delC, EPCAM deletion, HLA-B deletion, TAP1 p.(G646Vfs*12) c.1937delG, PSMB9 p.(R206*) c.616C>T, LARP4B p.(R692Ifs*83) c.2075_2076delGA, HNF1A p.(R159W) c.475C>T, NQO1 p.(P187S) c.559C>T, ARHGAP35 p.(F1247Lfs*5) c.3741delT, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ERBB2	p.(R678Q)	c.2033G>A	COSM436498	chr17:37879658	29.90%	NM_004448.4	missense
PIK3CA	p.(E453K)	c.1357G>A	COSM12584	chr3:178928079	23.79%	NM_006218.4	missense
RAD51	p.(R194*)	c.580C>T	.	chr15:41020955	25.45%	NM_133487.4	nonsense
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	28.55%	NM_000546.6	missense
APC	p.(R1687*)	c.5059C>T	.	chr5:112176350	9.56%	NM_000038.6	nonsense
CIC	p.(R1515H)	c.4544G>A	COSM303956	chr19:42799060	21.37%	NM_015125.5	missense
ERBB3	p.(A232V)	c.695C>T	COSM1242239	chr12:56481660	30.05%	NM_001982.4	missense
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	28.09%	NM_005245.4	frameshift Deletion
GNAS	p.(R201H)	c.602G>A	COSM27895	chr20:57484421	24.91%	NM_000516.7	missense
KEAP1	p.(R498*)	c.1492C>T	.	chr19:10600363	28.16%	NM_203500.2	nonsense
PIK3R1	p.(R358*)	c.1072C>T	.	chr5:67588981	27.75%	NM_181523.3	nonsense
PPP2R2A	p.(R153*)	c.457C>T	.	chr8:26217795	2.73%	NM_002717.4	nonsense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
SETD2	p.(R1407Gfs*5)	c.4219delA	.	chr3:47161906	25.06%	NM_014159.7	frameshift Deletion
SLX4	p.(D1424*)	c.4269_4270insT	.	chr16:3639369	22.62%	NM_032444.4	nonsense
TP53	p.(G245S)	c.733G>A	COSM6932	chr17:7577548	3.43%	NM_000546.6	missense
EPHA2	p.(P460Rfs*33)	c.1379delC	COSM294351	chr1:16462198	62.83%	NM_004431.5	frameshift Deletion
TAP1	p.(G646Vfs*12)	c.1937delG	.	chr6:32814947	28.18%	NM_000593.6	frameshift Deletion
PSMB9	p.(R206*)	c.616C>T	.	chr6:32827265	30.55%	NM_002800.5	nonsense
LARP4B	p.(R692Ifs*83)	c.2075_2076delGA	.	chr10:859006	30.31%	NM_015155.3	frameshift Deletion
HNF1A	p.(R159W)	c.475C>T	.	chr12:121426784	28.62%	NM_000545.8	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.40%	NM_000903.3	missense
ARHGAP35	p.(F1247Lfs*5)	c.3741delT	.	chr19:47440576	30.60%	NM_004491.5	frameshift Deletion
PGD	p.(Y202C)	c.605A>G	.	chr1:10471560	50.57%	NM_002631.4	missense
SPEN	p.(R345H)	c.1034G>A	.	chr1:16235968	29.42%	NM_015001.3	missense
JAK1	p.(T593M)	c.1778C>T	.	chr1:65313336	26.38%	NM_002227.4	missense
LRRC7	p.(P656S)	c.1966C>T	.	chr1:70494025	26.17%	NM_001370785.2	missense
BRINP3	p.(H55R)	c.164A>G	.	chr1:190423857	2.95%	NM_199051.3	missense
AKT3	p.(G342E)	c.1025G>A	.	chr1:243716169	19.62%	NM_005465.7	missense
AKT3	p.(?)	c.949-3_949-2insT	.	chr1:243716247	29.13%	NM_005465.7	unknown
DNMT3A	p.(G334S)	c.1000G>A	.	chr2:25470474	2.84%	NM_022552.5	missense
ASXL2	p.(R357Q)	c.1070G>A	.	chr2:25976475	25.66%	NM_018263.6	missense
SETD2	p.(G1644R)	c.4930G>A	.	chr3:47143033	4.50%	NM_014159.7	missense
DOCK3	p.(R501Q)	c.1502G>A	.	chr3:51264838	27.28%	NM_004947.5	missense
MAML3	p.(Q489Tfs*29)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	8.70%	NM_018717.5	frameshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	91.30%	NM_018717.5	frameshift Block Substitution
FAT1	p.(Y4540H)	c.13618T>C	.	chr4:187509895	35.42%	NM_005245.4	missense
FAT1	p.(D3360N)	c.10078G>A	.	chr4:187530465	12.75%	NM_005245.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ZFP2	p.(T265I)	c.794C>T	.	chr5:178359108	27.98%	NM_030613.4	missense
TAP2	p.(A609T)	c.1825G>A	.	chr6:32797284	26.21%	NM_018833.2	missense
LATS1	p.(M30R)	c.89T>G	.	chr6:150023174	28.55%	NM_004690.4	missense
ESR1	p.(K416Nfs*3)	c.1248delA	.	chr6:152382134	27.43%	NM_001122740.2	frameshift Deletion
FANCG	p.(R520H)	c.1559G>A	.	chr9:35075001	26.12%	NM_004629.2	missense
MEN1	p.(G205S)	c.613G>A	.	chr11:64575419	25.27%	NM_000244.3	missense
KMT2A	p.(R758del)	c.2274_2276delAAG	.	chr11:118344144	13.36%	NM_001197104.2	nonframeshift Deletion
ETV6	p.(R49H)	c.146G>A	.	chr12:11905496	12.75%	NM_001987.5	missense
ACVR1B	p.(A528T)	c.1582G>A	.	chr12:52387835	26.80%	NM_020328.4	missense
POLE	p.(A1557V)	c.4670C>T	.	chr12:133219464	26.76%	NM_006231.4	missense
FANCM	p.(R1719C)	c.5155C>T	.	chr14:45658380	27.10%	NM_020937.4	missense
AKT1	p.(V337M)	c.1009G>A	.	chr14:105239378	32.95%	NM_001014431.2	missense
MGA	p.(R291Q)	c.872G>A	.	chr15:41961964	4.77%	NM_001164273.1	missense
STARD9	p.(P2691S)	c.8071C>T	.	chr15:42981847	29.26%	NM_020759.3	missense
B2M	p.(A8D)	c.23C>A	.	chr15:45003767	29.19%	NM_004048.4	missense
B2M	p.(?)	c.346+1G>A	.	chr15:45007900	29.66%	NM_004048.4	unknown
ZFHX3	p.(P2582T)	c.7744C>A	.	chr16:72828837	29.89%	NM_006885.4	missense
ZFHX3	p.(S2067P)	c.6199T>C	.	chr16:72830382	28.88%	NM_006885.4	missense
SMAD2	p.(S467L)	c.1400C>T	.	chr18:45368202	31.62%	NM_001003652.4	missense
JAK3	p.(Y939C)	c.2816A>G	.	chr19:17942199	30.62%	NM_000215.4	missense
KMT2B	p.(R1846W)	c.5536C>T	.	chr19:36222907	10.90%	NM_014727.3	missense
ARHGAP35	p.(G449R)	c.1345G>A	.	chr19:47423277	26.20%	NM_004491.5	missense
ARHGAP35	p.(R1419H)	c.4256G>A	.	chr19:47503701	2.25%	NM_004491.5	missense
FLRT3	p.(L431P)	c.1292T>C	.	chr20:14306861	4.38%	NM_013281.3	missense
ENTPD6	p.(G4Vfs*26)	c.9delA	.	chr20:25187175	35.05%	NM_001247.5	frameshift Deletion
EP300	p.(R200Q)	c.599G>A	.	chr22:41513695	25.15%	NM_001429.4	missense
BCOR	p.(R74H)	c.221G>A	.	chrX:39934378	2.49%	NM_001123385.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MSH2	chr2:47630288	0.93	0.62
EPCAM	chr2:47596575	0.77	0.57

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0.64	0.52

Biomarker Descriptions

ERBB2 p.(R678Q) c.2033G>A

erb-b2 receptor tyrosine kinase 2

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[1]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases. However, ERBB2/HER2 is an orphan receptor with no known ligand. ERBB2 preferentially binds other ligand bound ERBB/HER family members to form hetero-dimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival[165]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[166,167,168].

Alterations and prevalence: ERBB2 gene amplification occurs in 10-20% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[3,4,5,6,8,9,10,169]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[9,170,171]. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772_A775dup.

Potential relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2[172,173]. Trastuzumab[174] was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab[175] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[176] (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer[177]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[178], with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib[179], an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib[179] in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbinitinib[180] was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line[90]. In 2024, a bispecific HER2 antibody, zanidatamab[181], was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. The vaccine, nelipepimut-S[182], was granted fast track designation by the FDA (2016) in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab[183] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, fast track designation was granted to the HER2-targeting antibody drug conjugate, amcenestrant[184], for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, zanidatamab[185], received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). In 2020, BDTX-189[186] received fast track designation for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion, and the humanized anti-HER2 antibody drug conjugate disitamab vedotin received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[187]. In 2021, the antibody-drug conjugate ARX788[188] received fast track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Additionally, fast track designation was granted to HER2-targeted chimeric antigen receptor macrophage (CAR-M) (2019), CT-0508[189], and to ex vivo gene-modified autologous chimeric antigen receptor-monocyte (CAR-Monocyte) cellular therapy (2024), CT-0525[190], for HER2-overexpressing solid tumors. In 2024, a small molecule inhibitor, BAY-2927088[191], received breakthrough designation for the treatment of NSCLC patients with ERBB2 activating mutations. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[192,193,194,195,196]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[197,198]. Additionally, acquired HER2

Biomarker Descriptions (continued)

mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[199]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[199]. Additionally, in 2024, FDA granted fast track designation to zongertinib[200], an irreversible ERBB2 tyrosine kinase inhibitor, for HER2-mutant NSCLC tumors that have progressed on or after platinum-based therapy.

PIK3CA p.(E453K) c.1357G>A

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[133]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[134,135]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[134]. 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[102,103]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[102,103,104,105]. 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[136,137,138].

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[8,9]. 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)[139,140]. 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[141,142,143]. 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[8,9].

Potential relevance: The PI3K inhibitor, alpelisib[144], 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[145]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[145]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[146]. The FDA also approved the kinase inhibitor, capivasertib (2023)[147] 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[148], 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[149,150].

MSH2 deletion

mutS homolog 2

Background: The MSH2 gene encodes the mutS homolog 2 protein[18]. MSH2 is a tumor suppressor gene that heterodimerizes with MSH6 to form the MutSα complex or with MSH3 to form the MutSβ complex[76]. Both MutS complexes function in DNA damage recognition of base-base mismatches or insertion/deletion (indels) mispairs[76]. Specifically, the MutSα complex recognizes 1-2 nucleotide indels while MutSβ recognizes longer indel mispairs[76]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication[76]. Mutations in MSH2 result in the degradation of MSH6[77]. Loss of MSH2 protein expression correlates with mutations in the genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[78]. MSH2, along with MLH1, MSH6, and PMS2, form the core components of the MMR pathway[79]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[80]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[79,81,82]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[79,83]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer.[81,83,84,85]. Specifically, MSH2 mutations are associated with an increased risk of ovarian and pancreatic cancer[86,87,88,89].

Alterations and prevalence: Somatic mutations in MSH2 are observed in 8% of uterine corpus endometrial carcinoma, as well as 2-3% of bladder urothelial carcinoma, melanoma, and colorectal adenocarcinoma[8,9]. Alterations in MSH2 are observed in pediatric cancers[8,9]. Somatic mutations are observed in 3% of soft tissue sarcoma, 1% of embryonal tumor, and less than 1% of B-lymphoblastic

Biomarker Descriptions (continued)

leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system tumors (1 in 1158 cases)[8,9].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[90]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[91,92]. MSH2 mutations are consistent with high grade in pediatric diffuse gliomas[93,94].

RAD51 p.(R194*) c.580C>T

RAD51 recombinase

Background: The RAD51 gene encodes the RAD51 recombinase protein and is a member of the RAD51 protein family that also includes RAD51B (RAD51L1), RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[95]. RAD51 interacts with many DNA repair and cell cycle genes, including BRCA1, BRCA2, p53, and ATM[96]. RAD51 is expressed in proliferating cells in the S or S/G2 phases of the cell cycle and mediates DNA strand invasion and homologous pairing between DNA duplexes[97,98]. RAD51 is a tumor suppressor gene. Loss of function mutations in RAD51 can lead to deficiencies in DSB repair and are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[97,99,100].

Alterations and prevalence: Somatic mutations in RAD51 have been described in breast and prostate cancers[96].

Potential relevance: Currently, no therapies are approved for RAD51 aberrations.

TP53 p.(G245S) c.733G>A, TP53 p.(R273H) c.818G>A

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[18]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[107]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[108]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[109,110].

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%)[8,9,111,112,113,114]. 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[8,9]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[115,116,117,118]. Alterations in TP53 are also observed in pediatric cancers[8,9]. 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)[8,9]. 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)[8,9].

Potential relevance: The small molecule p53 reactivator, PC14586[119] (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[120], (2019) and breakthrough designation[121] (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[122,123]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[124]. 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)[125,126,127,128,129,130]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[131]. 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[132].

Biomarker Descriptions (continued)

APC p.(R1687*) c.5059C>T

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[155]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[156,157]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[155,158]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[159].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[6,8,9]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[160,161].

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

CIC p.(R1515H) c.4544G>A

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[18,24]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[18,24]. 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[24]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[24].

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[8,9]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[8,9]. 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[24,25].

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[26,27].

ERBB3 p.(A232V) c.695C>T

erb-b2 receptor tyrosine kinase 3

Background: The ERBB3 gene encodes the erb-b2 receptor tyrosine kinase 3, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB3/HER3, EGFR/ERBB1/HER1, ERBB2/HER2, and ERBB4/HER4 make up the HER protein family[1]. ERBB3/HER3 binds to extracellular factors, such as neuregulins, but has an impaired kinase domain[2]. Upon ligand binding, ERBB3 forms hetero-dimers with other ERBB/HER family members, including ERBB2/HER2 resulting in activation of tyrosine kinase activity primarily through its dimerization partner.

Alterations and prevalence: ERBB3 gene amplification leading to an increase in expression occurs at low frequency (1-5%) in several cancer types including bladder, esophagus, lung adenocarcinoma, ovarian, pancreas, sarcoma, stomach, and uterine cancers[3,4,5,6,7,8,9]. ERBB3 is also the target of relatively frequent (5-10%) and recurrent somatic mutations in diverse cancer types including bladder, cervical, colorectal, and stomach cancers[3,6,8,9,10]. Recurrent ERBB3 mutations such as V104L/M, occur primarily in the extracellular domain.

Potential relevance: Currently, no therapies are approved for ERBB3 aberrations. Overexpression and activation of ERBB3/HER3 is one mechanism of acquired resistance to therapies targeting EGFR and ERBB2/HER2[11,12]. Preclinical and translational research studies have characterized the oncogenic potential of recurrent ERBB3 mutations and their sensitivity to anti-ERBB antibodies and small molecule inhibitors[13,14,15,16]. A phase I study exhibited progression-free survival (PFS) of 2.5 months and overall survival (OS) of 9 months in 25 patients with ERBB3 mutations treated by anti-ERBB antibodies or molecular-targeted agents[17].

Biomarker Descriptions (continued)

FAT1 p.(T2369Rfs*2) c.7105delA

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[18,37]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[37]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[37]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[37]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[37].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[8,9]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[8,9]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[8,9].

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

GNAS p.(R201H) c.602G>A

GNAS complex locus

Background: GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses.

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer (3%) as well as lung adenocarcinoma, colorectal, and gastric cancers (approximately 1%)[8,9,151,152]. In colorectal cancer, GNAS mutations were enriched in right-sided tumors[153]. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma[152]. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF.[152].

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib[154].

KEAP1 p.(R498*) c.1492C>T

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[18,72]. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2[73]. 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[73,74,75].

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[8,9].

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

PIK3R1 p.(R358*) c.1072C>T

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[18]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[101]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[101]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[101]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse

Biomarker Descriptions (continued)

reaction[102,103]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[102,103,104,105]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[106]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[101].

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

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

PPP2R2A p.(R153*) c.457C>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)[30,31]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[32]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[30].

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[30,31,33,34]. 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[8].

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[35], 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[30]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[36].

SETD2 p.(R1407Gfs*5) c.4219delA

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)[48,49]. 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[50]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[51,52]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[49]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[53]. 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[49,54].

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[8,54,55]. 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[8,48]. 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[48]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[48].

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)[56].

SLX4 p.(D1424*) c.4269_4270insT

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit[18]. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases[69]. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair[69,70,71]. Specifically, SLX4 localizes at DSB sites and recruits and

Biomarker Descriptions (continued)

interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1[69,70,71]. Germline SLX4 mutations are associated with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition[70].

Alterations and prevalence: Recurrent somatic mutations in SLX4 are observed in 11% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of stomach adenocarcinoma, and 4% of bladder urothelial carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for SLX4 aberrations.

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

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[18]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[43,44]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[44]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[43,44].

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

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

EPCAM deletion

epithelial cell adhesion molecule

Background: The EPCAM gene encodes epithelial cell adhesion molecule which is a type-1 transmembrane glycoprotein and carcinoma-associated antigen[18,45]. EPCAM mediates cell-to-cell adhesion by interacting with cell surface EPCAM molecules on neighboring cells[45]. EPCAM is observed to contribute to several biological processes involved in oncogenesis, including cell proliferation, differentiation, migration, and invasion[45,46]. Dysregulation, including overexpression, of EPCAM is commonly observed in a variety of cancer types[45]. However, germline deletion of EPCAM has been observed to result in MSH2 promoter hypermethylation and inactivation, which leads to Lynch syndrome, an autosomal dominant predisposition syndrome conferring predisposition to colorectal, endometrial, urothelial, sebaceous, central nervous system, ovarian and hepatobiliary neoplasms[47].

Alterations and prevalence: Somatic mutations in EPCAM are observed in 3% of uterine corpus endometrial carcinoma and 1% of skin cutaneous melanoma, lung adenocarcinoma, head and neck squamous cell carcinoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, and glioblastoma multiforme[8,9]. Biallelic loss of EPCAM is observed in less than 1% of uterine corpus endometrial carcinoma, sarcoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, colorectal adenocarcinoma, liver hepatocellular carcinoma, and kidney renal clear cell carcinoma[8,9]. Amplification of EPCAM is observed in 5% of uterine carcinosarcoma, 3% of lung squamous cell carcinoma, and 2% of bladder urothelial carcinoma, diffuse large B-cell lymphoma, and ovarian serous cystadenocarcinoma[8,9].

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[18]. 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[57]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[58]. 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[59,60,61]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[62].

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

Biomarker Descriptions (continued)

adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[8,9]. Biallelic loss of HLA-B is observed in 5% of DLBCL[8,9].

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

TAP1 p.(G646Vfs*12) c.1937delG

transporter 1, ATP binding cassette subfamily B member

Background: The TAP1 gene encodes the transporter 1, ATP binding cassette subfamily B member protein[18]. Along with TAP2 TAP1 is a member of the superfamily of ATP-binding cassette (ABC) transporters[18]. Together, TAP1 and TAP2 are capable of ATP-controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[19,20]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[21,22,23].

Alterations and prevalence: Somatic mutations in TAP1 are predominantly missense or truncating and have been observed in 6% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma and thymoma[8,9]. Biallelic deletion of TAP1 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[8,9].

Potential relevance: Currently, no therapies are approved for TAP1 aberrations.

PSMB9 p.(R206*) c.616C>T

proteasome subunit beta 9

Background: The PSMB9 gene encodes proteasome 20S subunit beta 9, a member of the proteasome B-type family, also known as the T1B family[18]. PSMB9, along with PSMB8 and PSMB10, functions as a beta subunit in the immunoproteasome (IP) protein complex to generate peptides for binding onto human leukocyte antigen (HLA) I molecules, which facilitates antigen presentation[162,163]. IP gene expression is inducible by interferon-gamma, a pleiotropic cytokine that exhibits a complex role in tumor immunity[162,164]. Loss of function of the immunoproteasome due to lack of subunit expression or down-regulation has been associated with a mesenchymal phenotype and may lead to immune evasion through antigen loss[163].

Alterations and prevalence: Somatic mutations in PSMB9 are observed in 2% of uterine corpus endometrial carcinoma[8,9]. Biallelic loss of PSMB9 is observed in 6% of diffuse large B-cell lymphoma[8,9].

Potential relevance: Currently, no therapies are approved for PSMB9 aberrations.

LARP4B p.(R692Ifs*83) c.2075_2076delGA

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[18]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[28]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[28]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[29].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[8,9]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

HNF1A p.(R159W) c.475C>T

HNF1 homeobox A

Background: The HNF1A gene encodes the HNF1 homeobox A transcription factor, part of the hepatocyte nuclear factor (HNF) family which also includes HNF1B, FOXA1/2/3, HNF4A/G and ONECUT1/2[63]. HNF proteins are required for the regulation of several liver-specific genes. Although enriched in the liver, HNF proteins are also expressed in a variety of tissues where they exhibit important roles in development and cell proliferation[63]. Specifically, HNF1A predominates in the liver, kidney, and pancreas and contains a DNA

Biomarker Descriptions (continued)

binding domain known to bind the inverted palindromic sequence GTTAATNATTANC[63]. HNF1A aberrations, including mutations and underexpression, that result in loss of HNF1A activity have been observed various cancer types including hepatocellular, endometrial, and pancreatic cancer[64,65,66]. However, HNF1A overexpression has been observed to drive pancreatic ductal adenocarcinoma (PDA) cell growth, suggesting multiple roles for HNF1A in cancer[67]. Germline mutations in HNF1A are linked to maturity-onset diabetes of the young (MODY3), which is associated with familial hepatic adenomatosis, a condition characterized by the presence multiple benign liver adenomas[68].

Alterations and prevalence: Somatic mutations in HNF1A are predominantly missense or truncating and occur in about 6% of uterine cancer, 4% of melanoma, and 2% of colorectal, bladder, liver, squamous lung, and stomach cancers[8,9].

Potential relevance: Currently, no therapies are approved for HNF1A aberrations.

ARHGAP35 p.(F1247Lfs*5) c.3741delT

Rho GTPase activating protein 35

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[18]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane[38,39]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[40,41].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[8,9]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[42]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[8,9]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[8,9].

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-04-16. For the most up-to-date information, search www.fda.gov.

ERBB2 p.(R678Q) c.2033G>A

BAY-2927088

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 activating mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to an oral small molecule tyrosine kinase inhibitor, BAY 2927088, for the treatment of patients with HER2 activating mutation in non-small cell lung cancer (NSCLC).

Reference:

https://www.biospace.com/article/releases/bayer-receives-u-s-fda-breakthrough-therapy-designation-for-bay-2927088-for-non-small-cell-lung-cancer-harboring-her2-activating-mutations

zongertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 activating mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the tyrosine kinase inhibitor, zongertinib (BI 1810631), for the treatment of adult patients with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 mutations and who have received prior systemic therapy.

Reference:

https://www.boehringer-ingelheim.com/us/human-health/cancer/boehringer-ingelheim-unveil-oncology-research-wclc

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,

Genes Assayed (continued)

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

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

ERBB2 p.(R678Q) c.2033G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	○	✖	○	✖	● (II)
neratinib	✖	○	✖	✖	✖
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II/III)
BAY-2927088	✖	✖	✖	✖	● (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

ERBB2 p.(R678Q) c.2033G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
zongertinib	✖	✖	✖	✖	● (II)
DF-1001, nivolumab	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
DS-1103a, trastuzumab deruxtecan	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)

PIK3CA p.(E453K) c.1357G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
inavolisib + palbociclib + fulvestrant	○	○	✖	✖	✖
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
ipatasertib, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (I)

MSH2 deletion

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

RAD51 p.(R194*) c.580C>T

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

TP53 p.(R273H) c.818G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

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

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 2025.05(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-04-16. NCCN information was sourced from www.nccn.org and is current as of 2025-04-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-04-16. ESMO information was sourced from www.esmo.org and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. 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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