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

Patient Name: 김국자
Gender: Female
Sample ID: N25-367

Primary Tumor Site: lung
Collection Date: 2025.12.18

Sample Cancer Type: Lung Cancer

Table of Contents

Report Highlights

5 Relevant Biomarkers
0 Therapies Available
22 Clinical Trials

Relevant Lung Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***0.95 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CCNE1 amplification* cyclin E1 Locus: chr19:30303647	None*	None*	11
IIC	*KRAS amplification* KRAS proto-oncogene, GTPase Locus: chr12:25362709	None*	None*	5
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*FLT3 amplification* fms related receptor tyrosine kinase 3 Locus: chr13:28578185	None*	None*	2

*** 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	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	2

* **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

*BCL6 amplification, CDKN1B deletion, MDM2 amplification, MSH6 p.(K1358Dfs*2) c.4068_4071dup, Microsatellite stable, PIK3R1 p.(D367Lfs*11) c.1099_1100delGA, RNASEH2B deletion, TET2 p.(M1333Rfs*31) c.3997_3998insGA, TP53 p.(P152L) c.455C>T, TP53 p.(R273L) c.818G>T, FAT1 deletion, TPMT amplification, POT1 deletion, NQO1 p.(P187S) c.559C>T, RPS6KB1 amplification, GNA13 amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MSH6	p.(K1358Dfs*2)	c.4068_4071dup	.	chr2:48033981	50.94%	NM_000179.3	frameshift Insertion
PIK3R1	p.(D367Lfs*11)	c.1099_1100delGA	.	chr5:67589007	41.97%	NM_181523.3	frameshift Deletion
TET2	p.(M1333Rfs*31)	c.3997_3998insGA	.	chr4:106182957	4.04%	NM_001127208.3	frameshift Insertion
TP53	p.(P152L)	c.455C>T	COSM10790	chr17:7578475	27.00%	NM_000546.6	missense
TP53	p.(R273L)	c.818G>T	COSM10779	chr17:7577120	48.46%	NM_000546.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	36.42%	NM_000903.3	missense
MAML3	p.(Q489Tfs*29)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	50.49%	NM_018717.5	frameshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	49.51%	NM_018717.5	frameshift Block Substitution
PIK3R1	p.(?)	c.1746-3_1746-2delCA	.	chr5:67591244	14.04%	NM_181523.3	unknown
NOTCH3	p.(G1347R)	c.4039G>C	.	chr19:15288700	73.01%	NM_000435.3	missense

Variant Details (continued)

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CCNE1	chr19:30303647	6.07	2.49
KRAS	chr12:25362709	5.01	2.1
ATM	chr11:108098341	1	0.69
FLT3	chr13:28578185	5.15	2.15
RB1	chr13:48877953	1.07	0.66
BCL6	chr3:187440209	5.59	2.31
CDKN1B	chr12:12870763	0.93	0.61
MDM2	chr12:69202958	7.37	2.96
RNASEH2B	chr13:51484145	1.05	0.65
FAT1	chr4:187509708	1.08	0.66
TPMT	chr6:18130879	6.12	2.51
POT1	chr7:124464001	1.1	0.67
RPS6KB1	chr17:57970507	5.38	2.24
GNA13	chr17:63010302	4.92	2.07
MET	chr7:116339789	1.12	0.68
FGFR1	chr8:38271452	1.04	0.65
RAD52	chr12:1022494	5.41	2.25
ETV6	chr12:11803059	5	2.09
SLCO1B3	chr12:21007974	1.1	0.67
ACVR1B	chr12:52345528	10.36	4.05
RNF43	chr17:56432226	4.49	1.91
PPM1D	chr17:58677747	4.66	1.97
AXIN2	chr17:63526027	4.44	1.89
PRKAR1A	chr17:66511464	4.82	2.03
SOX9	chr17:70117435	4.88	2.05
NOTCH3	chr19:15271451	4.79	2.02
ASXL1	chr20:30954155	7.07	2.85
NF2	chr22:29999923	12.19	4.72

Biomarker Descriptions

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2[57]. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2)

Biomarker Descriptions (continued)

which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein[57]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis[58,59,60]. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1[57,61].

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers[6]. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.[57,61,62].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[63], in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers[64,65,66].

KRAS amplification

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS[1]. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[2,3,4]. Germline mutations in KRAS lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features[5]. Somatic mutations in KRAS are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma[5].

Alterations and prevalence: The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[6,7,8]. Mutations at A59, K117, and A146 have also been observed but are less frequent[9,10]. Somatic mutations in KRAS are observed in 66% of pancreatic adenocarcinoma, 41% of colorectal adenocarcinoma, 30% of lung adenocarcinoma, 19% of uterine corpus endometrial carcinoma, 12% of uterine carcinosarcoma, 9% of stomach adenocarcinoma, 8% of testicular germ cell tumors, 6% of cholangiocarcinoma, 5% of cervical squamous cell carcinoma, acute myeloid leukemia, and diffuse large B-cell lymphoma, 4% of bladder urothelial carcinoma, and 2% of skin cutaneous melanoma and kidney renal papillary cell carcinoma[6,9]. KRAS is amplified in 9% of ovarian serous cystadenocarcinoma and testicular germ cell tumors, 8% of stomach adenocarcinoma , 7% of esophageal adenocarcinoma and uterine carcinosarcoma, 6% of lung adenocarcinoma, 4% of pancreatic adenocarcinoma and bladder urothelial carcinoma, 3% of lung squamous cell carcinoma, and 2% of sarcoma, mesothelioma, brain lower grade glioma, and uterine corpus endometrial carcinoma[6,9]. Alterations in KRAS are also observed in pediatric cancers[9]. Somatic mutations in KRAS are observed in 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of leukemia (29 in 354 cases), and in less than 1% of embryonal tumors (2 in 332 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[9]. KRAS is amplified in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[9]. Structural alterations in KRAS are observed in less than 1% of acute lymphoblastic leukemia (1 in 85 cases)[9].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[11] (2021) and adagrasib[12] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma[13]. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib[14] (2025), for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) after prior systemic therapy. The FDA has granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[15], for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib[16], and the KRAS G12C inhibitor, D3S-001[17], were both granted breakthrough therapy designation (2025) for KRAS G12C-mutated locally advanced or metastatic NSCLC in adults previously treated with chemotherapy and immunotherapy, excluding KRAS G12C inhibitors. The KRAS-G12C inhibitor, olomorasib[18], was granted breakthrough designation (2025) in combination with pembrolizumab[19] for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression ≥ 50%. The RAF/MEK clamp, avutometinib[20] was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC in patients who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520[21], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib[22], was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375[23], was also granted fast track designation (2025) for first-line and previously treated KRAS G12D-mutated locally advanced or metastatic pancreatic adenocarcinoma. The KRAS G12C inhibitor, D3S-001[24], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[25], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[26] and panitumumab[27], are contraindicated for treatment of colorectal

Biomarker Descriptions (continued)

cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[10]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[28].

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[103]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[104]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[104,105]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[106]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[107,108]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[109].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[6,9].

Potential relevance: The PARP inhibitor, olaparib[110] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[111] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[107,112,113]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[114]. However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM[115,116]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[117], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FLT3 amplification

fms related receptor tyrosine kinase 3

Background: The FLT3 gene encodes the fms related tyrosine kinase 3, a receptor that is a member of the class III receptor tyrosine kinase family, which also includes PDGFR, FMS, and KIT[151]. FLT3 is highly expressed in hematopoietic progenitor cells and is involved in hematopoietic expansion and normal development of dendritic cells[152]. Genomic alterations in FLT3 activate downstream oncogenic pathways, including the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, which promote cellular proliferation, survival, and inhibition of differentiation[151].

Alterations and prevalence: Somatic mutations occur in approximately 30% of acute myeloid leukemia (AML), 11% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of esophageal adenocarcinoma and lung adenocarcinoma, 3% of lung squamous cell carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of glioblastoma multiforme, bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[6,9,153,154,155]. The most common activating FLT3 mutations are internal tandem duplications (ITD) ranging from 3 to 400 base pairs in length within exons 14 and 15 in the juxtamembrane (JM) domain[156]. The second most frequent mutations are point mutations in exon 20 within the tyrosine kinase domain (TKD)[157]. FLT3 is amplified in 6% of colorectal adenocarcinoma and 2% of sarcoma, stomach adenocarcinoma, and esophageal adenocarcinoma[6,9,158]. Alterations in FLT3 are also observed in pediatric cancers[6,9]. Somatic mutations are observed in 7% of leukemia, 5% of soft tissue sarcoma, 3% of B- lymphoblastic leukemia/lymphoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), and peripheral nervous system cancers (2 in 1158 cases)[6,9]. FLT3 rearrangements occur in less than 1% of leukemia (1 in 107 cases) and are amplified in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[6,9].

Potential relevance: FLT3 rearrangements are recognized by the World Health Organization (WHO) as one of the possible molecular abnormality requirements that define myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions[159]. FLT3 rearrangements are associated with unfavorable or poor risk in adult and pediatric acute lymphoblastic leukemia[148,160,161]. The presence of a FLT3-ITD mutation or FLT3-TKD D835 mutation confers a poor prognosis in myelodysplastic syndrome (MDS)[43]. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML[146]. Midostaurin[162] (2017) and gilteritinib[163] (2018) are kinase inhibitors approved for AML patients with FLT3-ITD and TKD

Biomarker Descriptions (continued)

mutations, D835 and I836. Quizartinib dihydrochloride[164] (2023) is also a kinase inhibitor approved for AML patients with FLT3-ITD mutations. The FDA granted fast track designations to crenolanib[165] (2017) and tuspetinib (HM43239)[166] (2022) for FLT3 mutation-positive relapsed or refractory AML. A phase II trial testing crenolanib in 34 patients with FLT3-ITD and TKD mutated relapsed/refractory AML, reported that FLT3 inhibitor-naïve patients demonstrated a longer overall survival (OS) and event free survival (EFS) compared to previously treated patients (median OS: 55 weeks vs 13 weeks; median EFS: 13 weeks vs 7 weeks)[167]. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3-mutated AML reported a response rate of 86% and an average event-free survival of 45 months, with 77% of patients achieving complete remission[168]. Several multi-targeted tyrosine kinase inhibitors, such as sorafenib (2005), sunitinib (2006), cabozantinib (2012), and ponatinib (2012), are FDA-approved and include FLT3 as a target[169]. Sorafenib is recommended in combination with chemotherapy in FLT3-ITD mutated AML[170].

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer[67]. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[67,68]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[69]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[67,68,70]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[71].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in 20% of bladder urothelial carcinoma, 13% of uterine corpus endometrial carcinoma, and 10% of sarcoma and glioblastoma multiforme[6,9]. Biallelic loss of RB1 is also observed in several cancers including 15% of sarcoma, 10% of prostate adenocarciona, 9% of uterine carcinosarcoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma, 5% of liver hepatocellular carcinoma and adrenocortical carcinoma, and 4% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[6,9]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[72,73,74]. Alterations in RB1 are also observed in pediatric cancers[9]. Somatic mutations in RB1 are observed in 52% of retinoblastoma (16 in 31 cases), 3% of bone cancer (10 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (2 in 311 cases)[9]. Biallelic deletion of RB1 is observed in 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (28 in 731 cases), 3% of leukemia (7 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[9]. Structural variants in RB1 are observed in 3% of bone cancer (5 in 150 cases)[9].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

BCL6 amplification

B-cell CLL/lymphoma 6

Background: The BCL6 gene encodes the B-cell lymphoma 6 (BCL6) transcription repressor, a protein that is responsible for inhibiting the expression of several genes including those involved in the DNA damage response, cell cycle checkpoints, and modulating BCL2 expression[75,76,77]. BCL6 is most commonly expressed in germinal center B-cells and is required for germinal cell formation and affinity maturation during T-cell dependent antibody responses[76]. BCL6 is observed to competitively bind DNA motifs recognized by the oncogenic transcription factor STAT6, thereby repressing STAT6 mediated gene transcription[78,79]. Aberrations in BCL6 often lead to altered target gene transcription, including those involved in cell cycle arrest, differentiation, and apoptosis[75,76].

Alterations and prevalence: BCL6 rearrangement most commonly occurs with immunoglobulin H (IGH) partners and results in the truncation or removal the BCL6 promoter region and juxtaposition of BCL6 downstream of the partner gene promoter[80]. Replacement of the BCL6 promoter resulting from such translocations has been observed to lead to aberrant BCL6 expression[81]. BCL6 rearrangement is a common event in lymphoma and has been observed in up to 40% of diffuse large B-cell lymphoma (DLBCL) and 15% of follicle center lymphomas[76,80]. Somatic mutations in BCL6 are observed in 7% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of uterine carcinosarcoma, lung adenocarcinoma, and sarcoma[6,9]. Mutations in the 5' regulatory sequences of BCL6 are observed in 30-40% of germinal center B-cells and are believed to disrupt BCL6 negative autoregulation[76]. Amplifications are observed in 31% of lung squamous cell carcinoma, 16% of esophageal adenocarcinoma and ovarian serous cystadenocarcinoma, and 14% of head and neck and cervical squamous cell carcinoma, 9% of uterine carcinosarcoma, 6% of uterine corpus endometrial carcinoma, and 2-4% of stomach adenocarcinoma, diffuse large B-cell lymphoma, bladder urothelial carcinoma, breast invasive carcinoma, testicular germ cell tumors, liver hepatocellular carcinoma, and pancreatic adenocarcinoma[6,9]. Alterations in BCL6 are rare in pediatric cancers[6,9]. Somatic mutations in BCL6 are observed in 3% of soft tissue sarcoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), and

Biomarker Descriptions (continued)

glioma (1 in 297 cases)[6,9]. Amplification of BCL6 is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[6,9].

Potential relevance: B-cell lymphoma with BCL6 translocations that co-occur with MYC are referred to as double-hit lymphoma (DHL), while co-occurrence with MYC and BCL2 rearrangements is referred to as triple-hit lymphoma[82]. Such concomitant rearrangements are recognized by the World Health Organization (WHO) as diagnostic entity of diffuse large B-cell lymphoma/high grade B-cell lymphoma (HGBL) with MYC and BCL2 rearrangements[83]. DHL expressing BCL6 rearrangements are most often aggressive with poor prognosis, involve extra nodal sites, and have a germinal center phenotype[84,85].

CDKN1B deletion

cyclin dependent kinase inhibitor 1B

Background: The CDKN1B gene encodes the cyclin-dependent kinase inhibitor 1B protein and is also known as p27 or KIP1. CDKN1B belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1A (also known as WAF1/p21) and CDKN2C (also known as KIP2/p57)[48,49]. CDKN1B is involved in controlling G1/S cell cycle progression, cell proliferation, and apoptosis[1,48,49]. Specifically, in the nucleus, CDKN1B acts as a tumor suppressor by binding with the cyclin E-CDK2 and cyclin D-CDK4 complexes[50]. However, cytoplasmic localization of the CDKN1B/p27 is associated with invasiveness and metastasis in melanoma thereby giving it potential oncogenic function[51]. Germline mutations of CDKN1B are commonly associated with multiple endocrine neoplasia type 4 (MEN4), a hereditary disease characterized by parathyroid, anterior pituitary, or neuroendocrine tumors[49,52].

Alterations and prevalence: Somatic aberrations commonly observed in CDKN1B are mutations, copy number loss and amplification. Mutations that lead to a truncated form of CDKN1B are observed in 2% of endometrial carcinoma[6,9,49]. CDKN1B copy number loss is observed in 4% of prostate adenocarcinoma, and 2% of mature B-cell neoplasm[6,9]. Amplifications of CDKN1B are observed in 4% of ovarian epithelial tumors, 5% of seminoma, and 3% of non-seminomatous germ cell tumor[6,9].

Potential relevance: Currently, no targeted therapies are approved for CDKN1B aberrations.

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene[1]. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[29]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[29]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[30]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[30]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[30].

Alterations and prevalence: MDM2 is amplified in 19% of sarcoma, 9% of bladder urothelial carcinoma, 8% of glioblastoma multiforme, 7% of adrenocortical carcinoma, 5% of uterine carcinosarcoma, lung adenocarcinoma, esophageal adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and ovarian serous cystadenocarcinoma, 3% of breast invasive carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, testicular germ cell tumors, and lung squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma[6,9]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[31]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[32,33]. Somatic mutations in MDM2 are observed in 2% of uterine corpus endometrial carcinoma, adrenocortical carcinoma, and sarcoma[6,9]. Alterations in MDM2 are also observed in pediatric cancers[9]. Amplification of MDM2 is observed in 2% of bone cancer (1 in 42 cases), 1% of Wilms tumor (2 in 136 cases) and peripheral nervous system tumors (1 in 91 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[9]. Somatic mutations in MDM2 are observed in 2% of non-Hodgkin lymphoma (1 in 17 cases) and less than 1% of bone cancer (3 in 327 cases) and embryonal tumors (1 in 332 cases)[9].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[34].

MSH6 p.(K1358Dfs*2) c.4068_4071dup

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[86]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[86]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs

Biomarker Descriptions (continued)

mismatch errors which typically occur during DNA replication[86]. Mutations in MSH2 result in the degradation of MSH6[87]. MSH6, along with MLH1, MSH2, and PMS2, form the core components of the MMR pathway[86]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[86]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[88]. 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[89,90,91]. 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[89,92]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[90,92,93,94]. Specifically, MSH6 mutations are associated with an increased risk of ovarian and pancreatic cancer[95,96,97,98].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[6,9]. Alterations in MSH6 are observed in pediatric cancers[6,9]. Somatic mutations are observed in 9% of hepatobiliary cancer, 2% of T-lymphoblastic leukemia/lymphoma, 1% of B-lymphoblastic leukemia/lymphoma, and less than 1% of glioma (2 in 297 cases) and bone cancer (2 in 327 cases)[6,9].

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[19]. 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[99,100]. MSH6 mutations are consistent with high grade in pediatric diffuse gliomas[101,102].

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[171]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[90,92]. 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[91]. 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[172]. 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)[172]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[93,173,174,175,176]. 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[92]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[90,92,93,94].

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[90,92,177,178]. 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[177,178].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[19] (2014) and nivolumab[99] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[19] 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[19]. Dostarlimab[179] (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[174,180]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[100] (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[174,181,182]. 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[182]. 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[183,184]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[183,184].

PIK3R1 p.(D367Lfs*11) c.1099_1100delGA

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[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[124]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[124]. p85α is responsible for the binding, stabilization, and inhibition of the

Biomarker Descriptions (continued)

p110 catalytic subunit, thereby regulating PI3K activity[124]. 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 reaction[125,126]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[125,126,127,128]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[129]. 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[124].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 10% of glioblastoma multiforme, 6% of colorectal adenocarcinoma, 4% of brain lower grade glioma, and skin cutaneous melanoma, 3% of cervical squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, and breast invasive carcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, esophageal adenocarcinoma, thymoma, head and neck squamous cell carcinoma, and kidney chromophobe[6,9]. Additionally, biallelic loss of PIK3R1 is observed in 4% of prostate adenocarcinoma and 3% of ovarian serous cystadenocarcinoma[6,9]. Alterations in PIK3R1 are also observed in pediatric cancers[9]. Somatic mutations in PIK3R1 are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and leukemia (7 in 354 cases), 1% of glioma (3 in 297 cases) and bone cancer (3 in 327 cases), and less than 1% of embryonal tumors (2 in 332 cases) and peripheral nervous system tumors (1 in 1158 cases)[9]. Biallelic deletion of PIK3R1 is observed in 3% of leukemia (8 of 250 cases) and in less than 1% of B-lymphoblastic leukemia/lymphoma (4 of 731 cases), while structural alterations in PIK3R1 occur in fewer than 1% of leukemia (1 of 107 cases)[9].

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

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[35,36]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[35]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[35].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[6,9]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[6,9].

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

TET2 p.(M1333Rfs*31) c.3997_3998insGA

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,38]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[39,40]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[39,40]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[39,40]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[38,41,42].

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[43]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[41,44]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[6,9]. Alterations in TET2 are also observed in the pediatric population[9]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[9]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[9].

Biomarker Descriptions (continued)

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[45]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[46]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[47].

TP53 p.(P152L) c.455C>T, TP53 p.(R273L) c.818G>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[130]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[131]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[132,133].

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%)[6,9,134,135,136,137]. 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[6,9]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[138,139,140,141]. Alterations in TP53 are also observed in pediatric cancers[6,9]. 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)[6,9]. 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)[6,9].

Potential relevance: The small molecule p53 reactivator, PC14586[142] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[143,144]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[145]. 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)[43,45,146,147,148]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[149]. 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[150].

FAT1 deletion

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[1,37]. 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[6,9]. 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[6,9]. 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[6,9].

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

Biomarker Descriptions (continued)

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,185,186]. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine[185,186,187]. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure[185,187].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[6,9]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[6,9]. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[6,9]. Alterations in TPMT are also observed in pediatric cancers[9]. Somatic mutations are observed in less than 1% of peripheral nervous system tumors (1 in 1158 cases)[9]. Amplification of TPMT is observed in 1% of peripheral nervous system tumors (1 in 91 cases)[9].

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

POT1 deletion

protection of telomeres 1

Background: The POT1 gene encodes the protection of telomeres 1 protein, a nuclear protein and member of the Shelterin complex along with TERF1, TERF2, TPP1, TINF2, and TERF2IP[118]. The Shelterin complex is responsible for the protection and maintenance telomeres[1,118,119]. POT1 mediates the association of the Shelterin complex with single-stranded telomeric DNA, resulting in the prevention of telomerase binding and subsequent telomere elongation[118,120]. POT1 also inhibits inappropriate DNA damage response at telomeres by preventing the binding of RPA and inhibiting recruitment of ATR, thereby protecting telomeres from erroneous repair[119]. Loss of function POT1 germline mutations have been observed in melanoma, chronic lymphocytic leukemia (CLL), angiosarcoma, and glioma[119].

Alterations and prevalence: Somatic mutations in POT1 are observed in 5% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and lung squamous cell carcinoma[6,9].

Potential relevance: Currently, no therapies are approved for POT1 aberrations.

RPS6KB1 amplification

ribosomal protein S6 kinase B1

Background: The RPS6KB1 gene encodes ribosomal protein S6 kinase B1[1]. RPS6KB1, also known as S6K1, belongs to the AGC kinase family along with AKT, PKA, PKC, and PKG[53]. RPS6KB1 is a downstream target of mTORC1 phosphorylation which results in activation of RPS6KB1 and subsequent phosphorylation of the 40S ribosomal protein S6[54,55]. Aberrations including amplification and overexpression of RPS6KB1 have been associated with various cancer types including breast, kidney, and hepatocellular carcinoma, supporting an oncogenic role for RPS6KB1[54,56].

Alterations and prevalence: Somatic mutations in RPS6KB1 are observed in 2% uterine corpus endometrial carcinoma[6,9]. Amplification of RPS6KB1 is observed in 9% of breast invasive carcinoma, 5% of liver hepatocellular carcinoma and mesothelioma, and 4% uterine carcinosarcoma[6,9].

Potential relevance: Currently, no therapies are approved for RPS6KB1 aberrations.

GNA13 amplification

G protein subunit alpha 13

Background: The GNA13 gene encodes the G protein subunit α 13. GNA13 functions as the α subunit of heterotrimeric G proteins, which are responsible for binding guanine nucleotide, hydrolyzing GTP, and interacting with specific receptor and effector molecules[121]. Specifically, GNA13 mediated signaling is observed to impact several cellular processes including the regulation of cell

Biomarker Descriptions (continued)

growth, transformation, cell adhesion, and migration[122]. GNA13 deregulation, including overexpression, has been observed to result in increased levels of chemokines which can promote cell proliferation[121]. In contrast, mutations in GNA13 leading to inactivation result in B-cell release from germinal centers of lymphoid tissues to peripheral blood and may promote lymphomagenesis in germinal center diffuse large B-cell and Burkitt's lymphomas[123].

Alterations and prevalence: Somatic mutations in GNA13 are observed in 5% of DLBCL, 4% of uterine and 3% of bladder cancer[6,9]. Homozygous deletions are observed in 6% of DLBCL[6,9]. GNA13 is the most frequently mutated gene in germinal center derived B-cell lymphomas, including 25% of Burkitt lymphoma[123]. The majority of such mutations are predicted to result in loss of protein function[123].

Potential relevance: Currently, no therapies are approved for GNA13 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

CCNE1 amplification

camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1,

Genes Assayed (continued)

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

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

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
APR-1051	✖	✖	✖	✖	● (I/II)
ARTS-021	✖	✖	✖	✖	● (I/II)
ECI-830, hormone therapy, ribociclib	✖	✖	✖	✖	● (I/II)
INX-315, hormone therapy	✖	✖	✖	✖	● (I/II)
WJB-001	✖	✖	✖	✖	● (I/II)
ETX-197, hormone therapy	✖	✖	✖	✖	● (I)
lunresertib, camonsertib, Debio-0123	✖	✖	✖	✖	● (I)
nedisertib, tuvusertib	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

CCNE1 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
NKT-3964	✖	✖	✖	✖	● (I)
NKT-5097	✖	✖	✖	✖	● (I)

KRAS amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
JAB-23E73	✖	✖	✖	✖	● (I/II)
ASP-5834	✖	✖	✖	✖	● (I)
BBO-11818, pembrolizumab, cetuximab, chemotherapy	✖	✖	✖	✖	● (I)
BGB-53038	✖	✖	✖	✖	● (I)
darlifarnib	✖	✖	✖	✖	● (I)

ATM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
senaparib, IMP-9064	✖	✖	✖	✖	● (I/II)

FLT3 amplification

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

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)
CID-078	✖	✖	✖	✖	● (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	***16.76%***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
3. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
4. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
5. Johnson et al. Classification of KRAS-Activating Mutations and the Implications for Therapeutic Intervention. Cancer Discov. 2022 Apr 1;12(4):913-923. PMID: 35373279
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
7. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
8. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. J Med Life. 2014 Oct-Dec;7(4):581-7. PMID: 25713627
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
10. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
11. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf
12. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
13. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219616s000lbl.pdf
15. https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf
16. https://ir.revmed.com/node/11881/pdf
17. https://www.prnewswire.com/news-releases/d3-bio-inc-announces-fda-breakthrough-therapy-designation-and-orphan-drug-designation-for-d3s-001-for-the-treatment-of-patients-with-kras-g12c-mutated-cancers-302540808.html
18. https://www.prnewswire.com/news-releases/lillys-olomorasib-receives-us-fdas-breakthrough-therapy-designation-for-the-treatment-of-certain-newly-diagnosed-metastatic-kras-g12c-mutant-lung-cancers-302545643.html
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
20. https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination
21. https://www.businesswire.com/news/home/20250109170439/en/
22. https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy
23. https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375
24. https://www.d3bio.com/press-releases/d3-bios-d3s-001-receives-u-s-fda-fast-track-designation-for-the-treatment-of-colorectal-cancer-with-kras-g12c-mutation
25. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation-_July_2021.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf
28. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N. Engl. J. Med. 1990 Aug 30;323(9):561-5. PMID: 2199829
29. Toledo et al. MDM2 and MDM4: p53 regulators as targets in anticancer therapy. Int. J. Biochem. Cell Biol. 2007;39(7-8):1476-82. PMID: 17499002
30. Zhao et al. The regulation of MDM2 oncogene and its impact on human cancers. Acta Biochim. Biophys. Sin. (Shanghai). 2014 Mar;46(3):180-9. PMID: 24389645
31. Helei et al. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. Cancer Cell International volume 19, Article number: 216 (2019). PMID: 31440117
32. Dembla et al. Prevalence of MDM2 amplification and coalterations in 523 advanced cancer patients in the MD Anderson phase 1 clinic. Oncotarget. 2018 Sep 4;9(69):33232-33243. PMID: 30237864

References (continued)

33. Momand et al. The MDM2 gene amplification database. Nucleic Acids Res. 1998 Aug 1;26(15):3453-9. PMID: 9671804
34. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
35. D'Alessandro et al. BRCA2 controls DNA:RNA hybrid level at DSBs by mediating RNase H2 recruitment. Nat Commun. 2018 Dec 18;9(1):5376. PMID: 30560944
36. Aden et al. Epithelial RNase H2 Maintains Genome Integrity and Prevents Intestinal Tumorigenesis in Mice. Gastroenterology. 2019 Jan;156(1):145-159.e19. PMID: 30273559
37. Peng et al. Role of FAT1 in health and disease. Oncol Lett. 2021 May;21(5):398. PMID: 33777221
38. Pan et al. The TET2 interactors and their links to hematological malignancies. IUBMB Life. 2015 Jun;67(6):438-45. PMID: 26099018
39. An et al. TET family dioxygenases and DNA demethylation in stem cells and cancers. Exp. Mol. Med. 2017 Apr 28;49(4):e323. PMID: 28450733
40. Rasmussen et al. Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev. 2016 Apr 1;30(7):733-50. PMID: 27036965
41. Ko et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature. 2010 Dec 9;468(7325):839-43. PMID: 21057493
42. Solary et al. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014 Mar;28(3):485-96. PMID: 24220273
43. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
44. Kosmider et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood. 2009 Oct 8;114(15):3285-91. PMID: 19666869
45. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
46. Lundberg et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014 Apr 3;123(14):2220-8. PMID: 24478400
47. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
48. Chu et al. The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. Nat. Rev. Cancer. 2008 Apr;8(4):253-67. PMID: 18354415
49. Cusan et al. Landscape of CDKN1B Mutations in Luminal Breast Cancer and Other Hormone-Driven Human Tumors. Front Endocrinol (Lausanne) . 2018 Jul 17;9:393. PMID: 30065701
50. Bencivenga et al. p27 Kip1 and human cancers: A reappraisal of a still enigmatic protein. Cancer Lett. 2017 Sep 10;403:354-365. PMID: 28687353
51. Denicourt et al. Relocalized p27Kip1 tumor suppressor functions as a cytoplasmic metastatic oncogene in melanoma. Cancer Res. 2007 Oct 1;67(19):9238-43. PMID: 17909030
52. Alrezk et al. MEN4 and CDKN1B mutations: The latest of the MEN syndromes. Endocr. Relat. Cancer. 2017 Oct;24(10):T195-T208. PMID: 28824003
53. Tavares et al. The S6K protein family in health and disease. Life Sci. 2015 Jun 15;131:1-10. PMID: 25818187
54. Pópulo et al. The mTOR signalling pathway in human cancer. Int J Mol Sci. 2012;13(2):1886-918. PMID: 22408430
55. Mossmann et al. mTOR signalling and cellular metabolism are mutual determinants in cancer. Nat Rev Cancer. 2018 Dec;18(12):744-757. PMID: 30425336
56. Sinclair et al. The 17q23 amplicon and breast cancer. Breast Cancer Res Treat. 2003 Apr;78(3):313-22. PMID: 12755490
57. Hwang et al. Cyclin E in normal and neoplastic cell cycles. Oncogene. 2005 Apr 18;24(17):2776-86. PMID: 15838514
58. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
59. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
60. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
61. Schraml et al. Cyclin E overexpression and amplification in human tumours. J. Pathol. 2003 Jul;200(3):375-82. PMID: 12845634
62. Bai et al. Proliferation profile of classical Hodgkin's lymphomas. Increased expression of the protein cyclin D2 in Hodgkin's and Reed-Sternberg cells. Mod. Pathol. 2004 Nov;17(11):1338-45. PMID: 15354186
63. https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda

References (continued)

64. Keyomarsi et al. Cyclin E and survival in patients with breast cancer. N. Engl. J. Med. 2002 Nov 14;347(20):1566-75. PMID: 12432043
65. Zhao et al. Prognostic Values of CCNE1 Amplification and Overexpression in Cancer Patients: A Systematic Review and Meta-analysis. J Cancer. 2018;9(13):2397-2407. PMID: 30026836
66. Huang et al. Meta-analysis for cyclin E in lung cancer survival. Clin. Chim. Acta. 2012 Apr 11;413(7-8):663-8. PMID: 22244930
67. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev . 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
68. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. J. Clin. Invest. 2012 Feb;122(2):425-34. PMID: 22293180
69. Dyson. RB1: a prototype tumor suppressor and an enigma. Genes Dev. 2016 Jul 1;30(13):1492-502. PMID: 27401552
70. Cobrinik. Pocket proteins and cell cycle control. Oncogene. 2005 Apr 18;24(17):2796-809. PMID: 15838516
71. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam. Cancer. 2012 Jun;11(2):225-33. PMID: 22205104
72. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. Oman J Ophthalmol . May-Aug 2016;9(2):116-8. PMID: 27433042
73. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. Leukemia. 1999 Sep;13(9):1367-73. PMID: 10482987
74. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. Ophthalmology. 2007 Jul;114(7):1378-83. PMID: 17613328
75. Cardenas et al. The Expanding Role of the BCL6 Oncoprotein as a Cancer Therapeutic Target. Clin Cancer Res. 2017 Feb 15;23(4):885-893. PMID: 27881582
76. Pasqualucci et al. Mutations of the BCL6 proto-oncogene disrupt its negative autoregulation in diffuse large B-cell lymphoma. Blood. 2003 Apr 15;101(8):2914-23. PMID: 12515714
77. Liongue et al. B Cell Lymphoma 6 (BCL6): A Conserved Regulator of Immunity and Beyond. Int J Mol Sci. 2024 Oct 11;25(20). PMID: 39456751
78. Harris et al. Transcriptional repression of Stat6-dependent interleukin-4-induced genes by BCL-6: specific regulation of iepsilon transcription and immunoglobulin E switching. Mol Cell Biol. 1999 Oct;19(10):7264-75. PMID: 10490661
79. Delgado-Ramirez et al. Signal transducer and activator of transcription 6 as a target in colon cancer therapy. Oncol Lett. 2020 Jul;20(1):455-464. PMID: 32565970
80. Lossos et al. The BCL6 gene in B-cell lymphomas with 3q27 translocations is expressed mainly from the rearranged allele irrespective of the partner gene. Leukemia. 2003 Jul;17(7):1390-7. PMID: 12835729
81. Ye et al. Chromosomal translocations cause deregulated BCL6 expression by promoter substitution in B cell lymphoma. EMBO J. 1995 Dec 15;14(24):6209-17. PMID: 8557040
82. Beham-Schmid. Aggressive lymphoma 2016: revision of the WHO classification. Memo. 2017;10(4):248-254. PMID: 29250206
83. Alaggio et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748. PMID: 35732829
84. Raju K et al. Double-hit B-cell lymphomas with BCL6 and MYC translocations are aggressive, frequently extranodal lymphomas distinct from BCL2 double-hit B-cell lymphomas. Am J Sure Pathol. 2013 Mar;37(3):323-32. PMID: 23348205
85. Li et al. MYC/BCL6 double-hit lymphoma (DHL): a tumour associated with an aggressive clinical course and poor prognosis. Histopathology. 2016 Jun;68(7):1090-8. PMID: 26426741
86. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
87. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
88. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
89. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
90. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. Front Oncol. 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
91. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. Front Microbiol. 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133

References (continued)

92. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
93. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
94. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. J. Clin. Oncol. 2019 Feb 1;37(4):286-295. PMID: 30376427
95. Bonadona et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun 8;305(22):2304-10. PMID: 21642682
96. Engel et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106
97. Grant et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 Mar;148(3):556-64. PMID: 25479140
98. Hu et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018 Jun 19;319(23):2401-2409. PMID: 29922827
99. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
100. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
101. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430
102. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
103. Maréchal et al. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol. 2013 Sep 1;5(9). PMID: 24003211
104. Matsuoka et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007 May 25;316(5828):1160-6. PMID: 17525332
105. Ditch et al. The ATM protein kinase and cellular redox signaling: beyond the DNA damage response. Trends Biochem. Sci. 2012 Jan;37(1):15-22. PMID: 22079189
106. Kozlov et al. Autophosphorylation and ATM activation: additional sites add to the complexity. J. Biol. Chem. 2011 Mar 18;286(11):9107-19. PMID: 21149446
107. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. Endocr. Relat. Cancer. 2016 Jun;23(6):R267-85. PMID: 27226207
108. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
109. Cynthia et al. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016 Nov 25;11(1):159. PMID: 27884168
110. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
111. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
112. Gilardini Montani et al. ATM-depletion in breast cancer cells confers sensitivity to PARP inhibition. CR. PMID: 24252502
113. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin. Cancer Res. 2014 Feb 1;20(3):764-75. PMID: 24240112
114. Mateo et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N. Engl. J. Med. 2015 Oct 29;373(18):1697-708. PMID: 26510020
115. Naqvi et al. Heterogeneity of the Treatment Effect with PARP Inhibitors in Metastatic Castration-resistant Prostate Cancer: A Living Interactive Systematic Review and Meta-analysis. Eur Urol. 2025 Jun;87(6):626-640. PMID: 39848867
116. Evans et al. Exploring the Impact of Treatment Switching on Overall Survival from the PROfound Study in Homologous Recombination Repair (HRR)-Mutated Metastatic Castration-Resistant Prostate Cancer (mCRPC). Target Oncol. 2021 Sep;16(5):613-623. PMID: 34478046
117. https://www.senhwabio.com//en/news/20220125
118. Schmutz et al. Shelterin. Curr Biol. 2016 May 23;26(10):R397-9. PMID: 27218840
119. Wu et al. Role of POT1 in Human Cancer. Cancers (Basel). 2020 Sep 24;12(10). PMID: 32987645
120. Liu et al. PTOP interacts with POT1 and regulates its localization to telomeres. Nat Cell Biol. 2004 Jul;6(7):673-80. PMID: 15181449
121. Zhang et al. GNA13 promotes tumor growth and angiogenesis by upregulating CXC chemokines via the NF-κB signaling pathway in colorectal cancer cells. Cancer Med. 2018 Nov;7(11):5611-5620. PMID: 30267476

References (continued)

122. Worzfeld et al. G(12)/G(13)-mediated signalling in mammalian physiology and disease. Trends Pharmacol Sci. 2008 Nov;29(11):582-9. PMID: 18814923
123. Healy et al. GNA13 loss in germinal center B cells leads to impaired apoptosis and promotes lymphoma in vivo. Blood. 2016 Jun 2;127(22):2723-31. PMID: 26989201
124. Cheung et al. Targeting therapeutic liabilities engendered by PIK3R1 mutations for cancer treatment. Pharmacogenomics. 2016 Feb;17(3):297-307. PMID: 26807692
125. Cantley. The phosphoinositide 3-kinase pathway. Science. 2002 May 31;296(5573):1655-7. PMID: 12040186
126. Fruman et al. The PI3K Pathway in Human Disease. Cell. 2017 Aug 10;170(4):605-635. PMID: 28802037
127. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 2006 Aug;7(8):606-19. PMID: 16847462
128. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. Nat. Rev. Mol. Cell Biol. 2012 Feb 23;13(3):195-203. PMID: 22358332
129. Chagpar et al. Direct positive regulation of PTEN by the p85 subunit of phosphatidylinositol 3-kinase. Proc. Natl. Acad. Sci. U.S.A. 2010 Mar 23;107(12):5471-6. PMID: 20212113
130. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265
131. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
132. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602
133. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
134. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
135. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
136. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
137. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
138. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217
139. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514
140. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424
141. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566
142. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html
143. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
144. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
145. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. PMID: 34185076
146. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
147. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
148. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
149. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]

References (continued)

150. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829
151. Grafone et al. An overview on the role of FLT3-tyrosine kinase receptor in acute myeloid leukemia: biology and treatment. Oncol Rev. 2012 Mar 5;6(1):e8. PMID: 25992210
152. Kazi et al. FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. Physiol Rev. 2019 Jul 1;99(3):1433-1466. PMID: 31066629
153. Annesley et al. The Biology and Targeting of FLT3 in Pediatric Leukemia. Front Oncol. 2014;4:263. PMID: 25295230
154. Small. FLT3 mutations: biology and treatment. Hematology Am Soc Hematol Educ Program. 2006:178-84. PMID: 17124058
155. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013 May 30;368(22):2059-74. doi: 10.1056/NEJMoa1301689. Epub 2013 May 1. PMID: 23634996
156. Nakao et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996 Dec;10(12):1911-8. PMID: 8946930
157. Yamamoto et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood. 2001 Apr 15;97(8):2434-9. PMID: 11290608
158. Carow et al. Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. Blood. 1996 Feb 1;87(3):1089-96. PMID: 8562934
159. Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. PMID: 35732831
160. NCCN Guidelines® - NCCN-Pediatric Acute Lymphoblastic Leukemia [Version 1.2026]
161. Gutierrez-Camino et al. Characterisation of FLT3 alterations in childhood acute lymphoblastic leukaemia. Br J Cancer. 2024 Feb;130(2):317-326. PMID: 38049555
162. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/207997s010lbl.pdf
163. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211349s003lbl.pdf
164. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216993s001lbl.pdf
165. https://www.globenewswire.com/news-release/2017/12/01/1216122/0/en/Arog-Pharmaceuticals-Receives-FDA-Fast-Track-Designation-for-Crenolanib-in-Relapsed-or-Refractory-FLT3-Positive-AML.html
166. https://www.aptose.com/news-media/press-releases/detail/230/aptose-receives-fast-track-designation-for-hm43239-in
167. Jasleen K et al. Results of a Phase II Study of Crenolanib in Relapsed/Refractory Acute Myeloid Leukemia Patients (Pts) with Activating FLT3 Mutations. Blood. 124:389
168. Wang et al. Crenolanib and Intensive Chemotherapy in Adults With Newly Diagnosed FLT3-Mutated AML. J Clin Oncol. 2024 May 20;42(15):1776-1787. PMID: 38324741
169. Jeong et al. United States Food and Drug Administration approved oral kinase inhibitors for the treatment of malignancies. Curr Probl Cancer. 2013;37(3):110-44. PMID: 23972982
170. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2026]
171. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
172. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57. PMID: 9823339
173. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. Cancer Res. 2002 Jan 1;62(1):53-7. PMID: 11782358
174. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
175. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
176. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. Medicine (Baltimore). 2015 Dec;94(50):e2260. PMID: 26683947
177. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. Nat Commun. 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
178. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
179. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
180. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

References (continued)

181. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N. Engl. J. Med. 2003 Jul 17;349(3):247-57. PMID: 12867608

182. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann. Oncol. 2015 Jan;26(1):126-32. PMID: 25361982

183. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522

184. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031

185. Katara et al. TPMT Polymorphism: When Shield Becomes Weakness. Interdiscip Sci. 2016 Jun;8(2):150-155. PMID: 26297310

186. Yong et al. The role of pharmacogenetics in cancer therapeutics. Br J Clin Pharmacol. 2006 Jul;62(1):35-46. PMID: 16842377

187. McLeod et al. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. Leukemia. 2000 Apr;14(4):567-72. PMID: 10764140