		Approved Therapies			
Gene / Variant	**Allelic Fraction**	**Gastric Cancer**	**Other Indications**	**Associated With Resistance**	**Clinical Trials**
MRE11 c.689C>T p.P230L g.94471730G>A **Tier 2C** Likely Pathogenic	50.0% (of 229 reads)	-	-	-	2
POLE c.4337_4338delTG p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** Pathogenic	2.88% (of 139 reads)	trifluridine	cladribine clofarabine cytarabine daunorubicin	-	-
RNF43 c.813_825delGTGTGCCATCTGT p.C272fs*143 g.58360807_58360819delACAGATGGCACAC **Tier 2C** Likely Pathogenic	7.71% (of 441 reads)	-	-	-	1
TP53 c.743G>A p.R248Q g.7674220C>T **Tier 2C** Pathogenic	8.13% (of 246 reads)	-	acalabrutinib acalabrutinib /obinutuzumab alemtuzumab alemtuzumab /rituximab bortezomib /rituximab decitabine duvelisib fludarabine phosphate ibrutinib idelalisib idelalisib /rituximab lenalidomide	chlorambucil fludarabine lenalidomide rituximab	2

		Approved Therapies			
Gene / Variant	**Allelic Fraction**	**Gastric Cancer**	**Other Indications**	**Associated With Resistance**	**Clinical Trials**
			lenalidomide /rituximab obinutuzumab obinutuzumab /venetoclax ofatumumab rituximab rituximab /venetoclax venetoclax zanubrutinib		
ERBB2 c.346G>A p.V116M g.39708441G>A **Tier 3 Uncertain Significance**	47.0% (of 459 reads)	trastuzumab trastuzumab deruxtecan	afatinib bosutinib carboplatin /gemcitabine carboplatin /paclitaxel cisplatin /docetaxel cisplatin /gemcitabine cisplatin /paclitaxel cisplatin /pemetrexed dacomitinib docetaxel erlotinib gemcitabine lapatinib margetuximab mobocertinib neratinib osimertinib paclitaxel pemetrexed	-	-

		Approved Therapies			
Gene / Variant	**Allelic Fraction**	**Gastric Cancer**	**Other Indications**	**Associated With Resistance**	**Clinical Trials**
			pertuzumab trastuzumab emtansine tucatinib		
ERBB3 c.3380G>A p.R1127H g.56101239G>A **Tier 3 Uncertain Significance**	48.0% (of 629 reads)	-	afatinib bosutinib dacomitinib neratinib osimertinib	-	-
FGFR4 c.1871A>C p.N624T g.177096106A>C **Tier 3 Uncertain Significance**	48.0% (of 145 reads)	-	erdafitinib futibatinib infigratinib lenvatinib ponatinib regorafenib	-	-
JAK3 c.2660G>A p.R887H g.17832539C>T **Tier 3 Uncertain Significance**	58.0% (of 262 reads)	-	ruxolitinib	-	-

Variants of Unknown Clinical Significance

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
AMER1 c.1646G>A p.R549Q g.64191641C>T	6.43% (of 311 reads)	normal	**Tier 3**	**Uncertain Significance**
CRLF2 c.29C>T p.P10L g.1202520G>A	43.0% (of 326 reads)	loss	**Tier 3**	**Uncertain Significance**
EPCAM c.93C>G	36.0% (of 163 reads)	normal	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
p.N31K g.47373479C>G				
ERBB2 c.346G>A p.V116M g.39708441G>A	47.0% (of 459 reads)	loss	**Tier 3**	**Uncertain Significance**
ERBB3 c.3380G>A p.R1127H g.56101239G>A	48.0% (of 629 reads)	normal	**Tier 3**	**Uncertain Significance**
ERCC5 c.2108A>G p.D703G g.102865820A>G	48.0% (of 238 reads)	normal	**Tier 3**	**Uncertain Significance**
FAT1 c.3337G>A p.D1113N g.186663542C>T	38.0% (of 219 reads)	loss	**Tier 3**	**Uncertain Significance**
FGFR4 c.1871A>C p.N624T g.177096106A>C	48.0% (of 145 reads)	normal	**Tier 3**	**Uncertain Significance**
FUBP1 c.733C>G p.Q245E g.77964872G>C	52.0% (of 221 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-A c. 538_539delTTinsCA p.L180Q g.29943462_29943463delTTinsCA	100.0% (of 63 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-A c. 559_560delACinsCG p.T187R g.29943483_29943484delACinsCG	54.0% (of 119 reads)	normal	**Tier 3**	**Uncertain Significance**
HLA-A c. 570_571delGTinsCG p. E190_W191delinsDG	45.0% (of 152 reads)	loss	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
g.29943494_29943495delGTinsCG				
HLA-A c.899_900delTGinsCA p.L300P g.29944503_29944504delTGinsCA	51.0% (of 45 reads)	gain	**Tier 3**	**Uncertain Significance**
HLA-B c.419_420delACinsTA p.Y140L g.31356366_31356367delGTinsTA	48.0% (of 23 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-B c.362_363delGCinsCG p.S121T g.31356423_31356424delGCinsCG	86.0% (of 36 reads)	normal	**Tier 3**	**Uncertain Significance**
HLA-B c.354_357delCCTCinsTTGG p.L119W g.31356429_31356432delGAGGinsCCAA	81.0% (of 43 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-B c.313_314delCTinsGC p.L105A g.31356717_31356718delAGinsGC	98.0% (of 134 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-B c.282_283delGGinsCA p.Q94_A95delinsHT g.31356748_31356749delCCinsTG	100.0% (of 44 reads)	loss	**Tier 3**	**Uncertain Significance**
HLA-B c.204_206delAGAinsGAC p.E69T g.31356825_31356827delTCTinsGTC	70.0% (of 10 reads)	loss	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
HLA-C c.984_985delCAinsGG p.T329A g.31269996_31269997delTGinsCC	100.0% (of 181 reads)	gain	**Tier 3**	**Uncertain Significance**
HLA-C c.872_873delAAinsCG p.Q291P g.31270232_31270233delTTinsCG	97.0% (of 35 reads)	gain	**Tier 3**	**Uncertain Significance**
HLA-C c.559_560delACinsCT p.T187L g.31271132_31271133delGTinsAG	32.0% (of 236 reads)	loss	**Tier 3**	**Uncertain Significance**
JAK3 c.2660G>A p.R887H g.17832539C>T	58.0% (of 262 reads)	loss	**Tier 3**	**Uncertain Significance**
KMT2C c.2459C>T p.T820I g.152247975G>A	13.0% (of 528 reads)	loss	**Tier 3**	**Uncertain Significance**
KMT2C c.2291C>T p.S764F g.152248143G>A	7.33% (of 232 reads)	normal	**Tier 3**	**Uncertain Significance**
KMT2D c.1688C>A p.T563N g.49051995G>T	47.0% (of 157 reads)	normal	**Tier 3**	**Uncertain Significance**
NOTCH3 c.4793A>T p.D1598V g.15170769T>A	53.0% (of 590 reads)	normal	**Tier 3**	**Uncertain Significance**
PARP1 c.1873G>A p.A625T g.226377176C>T	47.0% (of 147 reads)	normal	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
PRKCI c.853G>A p.V285M g.170280374G>A	7.26% (of 634 reads)	loss	**Tier 3**	**Uncertain Significance**
RNF43 c.925T>A p.C309S g.58360176A>T	11.0% (of 284 reads)	loss	**Tier 3**	**Uncertain Significance**
SMC3 c.2164G>A p.E722K g.110598186G>A	7.45% (of 470 reads)	normal	**Tier 3**	**Uncertain Significance**
TENT5C c.354C>A p.N118K g.117623222C>A	45.0% (of 213 reads)	normal	**Tier 3**	**Uncertain Significance**
ZFHX3 c.2282G>T p.G761V g.72957864C>A	49.0% (of 211 reads)	loss	**Tier 3**	**Uncertain Significance**

Therapeutic Implications for Gastric Cancer

Therapies	Gene / Variant	Response	Therapies Description
trifluridine	***POLE*** p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** Pathogenic	Sensitive	-
trastuzumab	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Trastuzumab, a HER2/neu receptor antagonist, is FDA-approved for treating HER2-overexpressing breast cancer, and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma (patients are selected for therapy based on an FDA-approved companion diagnostic for trastuzumab); trastuzumab is EMA-approved for treating adult patients with HER2 positive metastatic breast cancer as monotherapy for those who have received at least two chemotherapy regimens for their metastatic disease (prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments; hormone receptor positive patients must also have failed hormonal therapy, unless patients are

Therapies	Gene / Variant	Response	Therapies Description
			unsuitable for these treatments); in combination with paclitaxel for treating adult patients with HER2 positive metastatic breast cancer who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable; in combination with docetaxel for treating adult patients with HER2 positive metastatic breast cancer who have not received chemotherapy for their metastatic disease; in combination with an aromatase inhibitor for treating postmenopausal patients with hormone-receptor positive HER2 positive metastatic breast cancer, not previously treated with trastuzumab; for treating adult patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable); in combination with paclitaxel or docetaxel for treating adult patients with HER2 positive early breast cancer following adjuvant chemotherapy with doxorubicin and cyclophosphamide; in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin for treating adult patients with HER2 positive early breast cancer; in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy for HER2 positive early breast cancer that is locally advanced (including inflammatory) or with tumours >2 cm in diameter; and in combination with capecitabine or 5-fluorouracil and cisplatin for treating adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received anti-cancer treatment for their metastatic disease.
trastuzumab deruxtecan	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Fam-trastuzumab deruxtecan-nxki, a HER2-directed antibody and topoisomerase inhibitor conjugate, is FDA-approved for treating adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either: in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy; unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy; unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy; and locally advanced or metastatic

Therapies	Gene / Variant	Response	Therapies Description
			HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen; trastuzumab deruxtecan is EMA-approved for treating adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

Therapeutic Implications for Other Indications

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
cetuximab	***TMB-low*** **Tier 2C Uncertain Significance** ***MS-stable*** **Tier 2C Uncertain Significance**	Sensitive	Cetuximab, an epidermal growth factor receptor antagonist, is FDA-approved for treating patients with locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU; recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy; KRAS wild-type, EGFR-expressing, metastatic colorectal cancer in combination with FOLFIRI for first-line treatment, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan; cetuximab is EMA-approved for treating patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan; squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.
ipilimumab/ nivolumab	***TMB-low*** **Tier 2C Uncertain Significance**	Sensitive	Nivolumab, a PD-1 blocking antibody, in combination with ipilimumab, a CTLA-4 blocking antibody, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma; for treating adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with 2 cycles of platinum-doublet chemotherapy; for treating adult patients with

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			unresectable malignant pleural mesothelioma, as first-line treatment; and for treating patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment; nivolumab, in combination with ipilimumab, is FDA-approved for treating adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment; for treating adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib; and unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment; nivolumab, in combination with ipilimumab, is EMA-approved for treating adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy; and for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.
5-fluorouracil	***MS-stable*** **Tier 2C** **Uncertain Significance**	Sensitive	5-fluorouracil is an antimetabolite fluoropyrimidine analog of the nucleoside pyrimidine. Fluorouracil is converted in vivo to active metabolites which block DNA and RNA synthesis, thereby inhibiting cell growth. Fluorouracil is used to treat several types of cancer including colon, rectal, and head and neck cancers.
5-fluorouracil/ leucovorin	***MS-stable*** **Tier 2C** **Uncertain Significance**	Sensitive	-
5-fluorouracil/ leucovorin/ oxaliplatin	***MS-stable*** **Tier 2C** **Uncertain Significance** ***KRAS*** p.G12A g.25245350C>G	Sensitive	Leucovorin, oxaliplatin and fluorouracil are chemotherapeutic drugs used in combination to treat colorectal cancer. This treatment regimen is known as FOLFOX.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Tier 2C **Pathogenic**		
capecitabine	***MS-stable*** **Tier 2C** **Uncertain Significance**	Sensitive	Capecitabine, a nucleoside metabolic inhibitor, is FDA- and EMA-approved for the adjuvant treatment of patients with Dukes' grade C colon cancer; for treating patients with metastatic colorectal cancer as first-line monotherapy when treatment with fluoropyrimidine therapy alone is preferred; as monotherapy for metastatic breast cancer resistant to both an anthracycline-containing regimen and taxanes (paclitaxel or docetaxel); and in combination with docetaxel for treating metastatic breast cancer after failure of prior anthracycline-containing therapy; capecitabine is also EMA-approved for the first-line treatment of patients with advanced gastric cancer in combination with a platinum-based regimen.
capecitabine/ oxaliplatin	***MS-stable*** **Tier 2C** **Uncertain Significance** ***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Capecitabine and oxaliplatin are chemotherapeutic drugs used in combination to treat advanced colorectal cancer. This treatment regimen is known as CAPOX.
fluoropyrimidine	***MS-stable*** **Tier 2C** **Uncertain Significance** ***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	-
lenvatinib/ pembrolizumab	***MS-stable*** **Tier 2C** **Uncertain Significance**	Sensitive	Lenvatinib, a kinase inhibitor, in combination with pembrolizumab, a programmed death receptor-1 (PD-1)-blocking antibody, is FDA- and EMA-approved for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC); lenvatinib, in combination with pembrolizumab, is FDA-approved for treating patients with advanced endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			candidates for curative surgery or radiation; lenvatinib, in combination with pembrolizumab, is EMA-approved for treating adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.
5-fluorouracil/ irinotecan/ leucovorin	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Leucovorin, irinotecan and fluorouracil are chemotherapeutic drugs used in combination to treat advanced colorectal cancer. This treatment regimen is known as FOLFIRI.
EGFR tyrosine kinase inhibitor	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	FDA-approved EGFR tyrosine kinase inhibitors include erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib.
afatinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Afatinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test, as first-line treatment; metastatic, squamous NSCLC progressing after platinum-based chemotherapy; afatinib is EMA-approved for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation (s) who are EGFR TKI-naïve; and locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum based chemotherapy.
aflibercept	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Aflibercept, a vascular endothelial growth factor inhibitor, in combination with 5-fluorouracil, leucovorin, and irinotecan, is FDA- and EMA-approved for treating patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.
atezolizumab	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, is FDA- and EMA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			tumor area), as determined by an FDA-approved test; for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations; as a single-agent for treating adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab); in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC); and, in combination with bevacizumab, for treating patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy; atezolizumab is FDA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status; stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test, as adjuvant treatment following resection and platinum-based chemotherapy; in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations; and, in combination with cobimetinib and vemurafenib, for treating patients with BRAF V600 mutation-positive unresectable or metastatic melanoma; atezolizumab is EMA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy; in combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) (in patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			appropriate targeted therapies); and, in combination with nab-paclitaxel, for treating adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.
bevacizumab	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Bevacizumab, a VEGF-specific angiogenesis inhibitor, is FDA- and EMA-approved for treating patients with metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment; metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment; metastatic renal cell carcinoma, in combination with interferon alfa; persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan; stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection, in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent; patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan; patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by bevacizumab as a single agent; bevacizumab is FDA-approved for treating adult patients with recurrent glioblastoma; and in combination with atezolizumab, for treating patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy; bevacizumab is EMA-approved for treating adult patients with metastatic breast cancer, in combination with paclitaxel for first-line treatment; metastatic breast cancer, in combination with capecitabine for first-line treatment of adult patients in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			(patients who have received taxane and anthracycline containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine); unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with EGFR activating mutations, in combination with erlotinib for first-line treatment.
binimetinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Binimetinib, a kinase inhibitor, in combination with encorafenib, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.
carboplatin/ gemcitabine	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Gemcitabine in combination with carboplatin is approved for the treatment of patients with advanced ovarian cancer that has relapsed at least six months after completion of platinum-based therapy.
carboplatin/ paclitaxel	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Carboplatin and paclitaxel are chemotherapeutic drugs used in combination to treat endometrial, ovarian, and head and neck cancers, and non-small cell lung cancer that has spread.
cetuximab	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Cetuximab, an epidermal growth factor receptor antagonist, is FDA-approved for treating patients with locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU; recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy; KRAS wild-type, EGFR-expressing, metastatic colorectal

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			cancer in combination with FOLFIRI for first-line treatment, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan; cetuximab is EMA-approved for treating patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan; squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.
cisplatin	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Cisplatin, a cytotoxic heavy metal chemotherapeutic agent, is FDA-approved for treating patients with a metastatic testicular tumor in established combination therapy with other approved chemotherapeutic agents who have already received appropriate surgical and/or radiotherapeutic procedures, metastatic ovarian tumor in established combination therapy with other approved chemotherapeutic agents who have already received appropriate surgical and/or radiotherapeutic procedures, and transitional cell bladder cancer which is no longer amenable to local treatments as a single agent .
cisplatin/ docetaxel	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	-
cisplatin/ gemcitabine	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Gemcitabine is approved for use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced, or metastatic non-small cell lung cancer.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	ERBB2 p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**		
cisplatin/ paclitaxel	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Cisplatin is a cytotoxic heavy metal chemotherapeutic agent. Paclitaxel is a natural product which disrupts the normal interphase and mitotic cellular functions of the microtubule network. Paclitaxel is indicated in combination with cisplatin as first-line therapy for the treatment of advanced carcinoma of the ovary. The drug is also indicated in combination with cisplatin for the first-line treatment of non-small cell lung cancer.
cisplatin/ pemetrexed	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	-
cobimetinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Cobimetinib, a kinase inhibitor, in combination with vemurafenib, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
crizotinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Crizotinib, a kinase inhibitor, is FDA- and EMA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test; crizotinib is FDA-approved for treating pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive; and for treating adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
docetaxel	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Docetaxel, a microtubule inhibitor, is FDA- and EMA-approved for treating patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) as a single agent after platinum therapy failure, and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC; in combination with prednisone for treating metastatic castration-resistant prostate cancer (CRPC); in combination with cisplatin and fluorouracil for untreated, advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction; and in combination with cisplatin and fluorouracil for the induction treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN); docetaxel is FDA-approved for treating patients with locally advanced or metastatic breast cancer after chemotherapy failure as a single agent, and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive breast cancer; docetaxel is EMA-approved for the adjuvant treatment of patients with operable node-positive breast cancer and operable node-negative breast cancer in combination with doxorubicin and cyclophosphamide (for patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer); in combination with doxorubicin for treating patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition; locally advanced or metastatic breast cancer as monotherapy after failure of cytotoxic therapy (previous chemotherapy should have included an anthracycline or an alkylating agent); in combination with trastuzumab for treating patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease; in combination with capecitabine for treating patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy (previous therapy should have included an anthracycline); and in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for treating patients with metastatic hormone-sensitive prostate cancer.
erlotinib	***KRAS*** p.G12A	Resistance	Erlotinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	g.25245350C>G **Tier 2C** Pathogenic		cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen; and for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine; erlotinib is EMA-approved for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations for the first-line treatment; locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease for switch maintenance treatment after first-line chemotherapy; locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (in patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable); and metastatic pancreatic cancer, in combination with gemcitabine.
gefitinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** Pathogenic	Resistance	Gefitinib, a tyrosine kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
gemcitabine	***KRAS*** p.G12A g.25245350C>G **Tier 2C** Pathogenic ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Gemcitabine, a nucleoside metabolic inhibitor, is FDA-approved as a single agent for treating patients with pancreatic cancer; in combination with carboplatin, for treating relapsed advanced ovarian cancer previously treated with platinum-based therapy; in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy unless anthracyclines were clinically contraindicated; and in combination with cisplatin, for treating non-small cell lung cancer.
osimertinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** Pathogenic	Resistance	Osimertinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test;

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			osimertinib is FDA-approved for treating adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, as adjuvant therapy after tumor resection; and metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy; osimertinib is EMA-approved for treating adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as adjuvant treatment after complete tumour resection; and locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
paclitaxel	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Paclitaxel, a microtubule inhibitor, is FDA- and EMA-approved for treating patients with metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy including an anthracycline unless clinically contraindicated; locally advanced or metastatic non-small cell lung cancer as first-line treatment in combination with carboplatin or cisplatin for those who are not candidates for curative surgery or radiation therapy; metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine; paclitaxel is also FDA-approved for treating patients with advanced carcinoma of the ovary as subsequent therapy and as first-line therapy in combination with cisplatin; node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy; and AIDS-related Kaposi's sarcoma as second-line treatment; paclitaxel is also EMA-approved in combination with carboplatin for treating adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer.
panitumumab	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Panitumumab, an epidermal growth factor receptor (EGFR) antagonist, is FDA- and EMA-approved for treating patients with wild-type RAS (defined as wild-type in both KRAS and NRAS) metastatic colorectal cancer in combination with FOLFOX for first-line treatment, as monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy; and panitumumab is EMA-approved for treating patients with wild-type RAS metastatic colorectal cancer in first-line in

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			combination with FOLFIRI, and in second-line in combination with FOLFIRI for those who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
pemetrexed	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Pemetrexed, a folate analog metabolic inhibitor, is FDA- and EMA-approved for treating patients with locally advanced or metastatic nonsquamous non-small cell lung cancer as initial treatment in combination with cisplatin, or single-agent maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy, or as a single-agent after prior chemotherapy for patients with recurrent, metastatic, nonsquamous non-small cell lung cancer, and for malignant pleural mesothelioma as initial treatment in combination with cisplatin for patients whose disease is unresectable or who are otherwise not candidates for curative surgery; pemetrexed is also FDA-approved for treating patients with metastatic, nonsquamous non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as initial treatment in combination with pembrolizumab and platinum chemotherapy.
ramucirumab	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Ramucirumab, a VEGFR2 antagonist, is FDA- and EMA-approved, as a single agent or in combination with paclitaxel, for treating patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy; in combination with erlotinib, for first-line treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations; in combination with docetaxel, for treating patients with metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving ramucirumab); in combination with FOLFIRI, for treating patients with metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine; and, as a single agent, for treating patients with hepatocellular carcinoma who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
regorafenib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic** ***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Regorafenib, a kinase inhibitor, is FDA- and EMA-approved for treating patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy; locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) in patients who have been previously treated with imatinib mesylate and sunitinib malate; hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib.
selumetinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Selumetinib, a kinase inhibitor, is FDA-approved for treating pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).
sotorasib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Sotorasib, an inhibitor of the RAS GTPase family, is FDA-approved for treating adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.
tipiracil	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	-
trametinib	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Sensitive	Trametinib, a kinase inhibitor, is FDA- and EMA-approved as a single agent for treating BRAF-inhibitor treatment-naive patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test; in combination with dabrafenib for treating patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test; for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection; and for treating patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test; trametinib, in combination with dabrafenib, is FDA-approved for treating patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			with no satisfactory locoregional treatment options; and for treating adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.
vinorelbine	***KRAS*** p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Resistance	Vinorelbine, a vinca alkaloid, is FDA-approved in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer and as a single agent for the first-line treatment of patients with metastatic non-small cell lung cancer.
cladribine	***POLE*** p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** **Pathogenic**	Sensitive	Cladribine, a purine analog, is EMA-approved for treating patients with Hairy Cell Leukemia.
clofarabine	***POLE*** p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** **Pathogenic**	Sensitive	Clofarabine, a purine nucleoside metabolic inhibitor, is FDA- and EMA-approved for treating pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.
cytarabine	***POLE*** p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** **Pathogenic**	Sensitive	Cytarabine, a nucleoside metabolic inhibitor, and daunorubicin, an anthracycline topoisomerase inhibitor, are FDA- and EMA-approved for treating adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
daunorubicin	***POLE*** p.V1446fs*3 g.132643513_132643514delCA **Tier 2C** **Pathogenic**	Sensitive	Daunorubicin, a TOP2 and POR inhibitor, is FDA-approved for treating patients with acute monocytic leukemia and acute erythroid leukemia.
acalabrutinib	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Acalabrutinib, a kinase inhibitor, is FDA-approved for treating adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy; and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
acalabrutinib/ obinutuzumab	***TP53*** p.R248Q g.7674220C>T	Sensitive	-

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Tier 2C **Pathogenic**		
alemtuzumab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Alemtuzumab, a CD52-directed cytolytic monoclonal antibody, is FDA-approved for treating patients with B-cell chronic lymphocytic leukemia.
alemtuzumab/ rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Alemtuzumab, a CD52-directed cytolytic monoclonal antibody, in combination with rituximab, a CD20-directed cytolytic antibody, is NCCN-recommended as a first-line treatment option for chronic lymphocytic leukemia with del(17p) or TP53 mutation, when treatment with a BTK inhibitor or venetoclax is not deemed appropriate. The combination of alemtuzumab and rituximab is also NCCN-recommended as a relapsed/refractory therapy option for chronic lymphocytic leukemia with or without del(17p)/TP53 mutation.
bortezomib/ rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Bortezomib, a proteasome inhibitor, in combination with rituximab, a CD20-directed cytolytic antibody, and cyclophosphamide, an alkylating drug, and doxorubicin, an anthracycline topoisomerase inhibitor, and prednisone, a corticosteroid, is EMA-approved for treating adult patients with previously untreated mantle cell lymphoma, who are unsuitable for haematopoietic stem cell transplantation.
chlorambucil	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Resistance	-
decitabine	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Decitabine, a nucleoside metabolic inhibitor, is FDA-approved for treating patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate -2, and high-risk International Prognostic Scoring System groups; and EMA-approved for treating patients with newly diagnosed

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			de novo or secondary acute myeloid leukaemia (AML) who are not candidates for standard induction chemotherapy.
duvelisib	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Duvelisib, a kinase inhibitor, is FDA-approved for treating adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, and relapsed or refractory follicular lymphoma after at least two prior systemic therapies.
fludarabine	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Resistance	-
fludarabine phosphate	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Fludarabine phosphate, a nucleotide metabolic inhibitor, is FDA-approved for treating patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.
ibrutinib	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Ibrutinib, a kinase inhibitor, is FDA-approved for treating adult patients with mantle cell lymphoma who have received at least one prior therapy; chronic lymphocytic leukemia; small lymphocytic lymphoma; chronic lymphocytic leukemia with 17p deletion; small lymphocytic lymphoma with 17p deletion; Waldenström's macroglobulinemia; marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy; for treating adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy; ibrutinib is EMA-approved for treating adult patients with relapsed or refractory mantle cell lymphoma; previously untreated chronic lymphocytic leukaemia, as a single agent or in combination with rituximab or obinutuzumab or venetoclax; chronic lymphocytic leukaemia who have received at least one prior therapy, as a single agent or in combination with bendamustine and rituximab; Waldenström's macroglobulinaemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy; and in combination with rituximab, for treating adult patients with Waldenström's macroglobulinaemia.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
idelalisib	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Idelalisib, a kinase inhibitor, is FDA-approved for treating patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies; relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies; idelalisib, in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab), is EMA-approved for treating adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies; and as monotherapy for treating adult patients with follicular lymphoma that is refractory to two prior lines of treatment.
idelalisib/ rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Idelalisib, a kinase inhibitor, in combination with rituximab, a CD20-directed cytolytic antibody, is FDA-approved for treating patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; idelalisib, in combination with rituximab, is EMA-approved for treating adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.
lenalidomide	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Resistance	Lenalidomide, a thalidomide analogue, is FDA- and EMA-approved for treating patients with relapsed or progressed mantle cell lymphoma previously treated with two therapies including bortezomib, multiple myeloma in combination with dexamethasone, multiple myeloma as maintenance following autologous hematopoietic stem cell transplantation, and transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; lenalidomide, as combination therapy, is also EMA-approved for treating adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
lenalidomide	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Lenalidomide, a thalidomide analogue, is FDA- and EMA-approved for treating patients with relapsed or progressed mantle cell lymphoma previously treated with two therapies including bortezomib, multiple myeloma in combination with dexamethasone, multiple myeloma as maintenance following autologous hematopoietic stem cell transplantation, and transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; lenalidomide, as combination therapy, is also EMA-approved for treating adult patients with previously untreated multiple myeloma who are not eligible for transplant.
lenalidomide/ rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Lenalidomide, a thalidomide analogue, in combination with rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating patients with previously treated follicular lymphoma (FL); lenalidomide, in combination with rituximab, is FDA-approved for treating patients with previously treated marginal zone lymphoma (MZL).
obinutuzumab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Obinutuzumab, a CD20-directed cytolytic antibody, in combination with chlorambucil, is FDA- and EMA-approved for treating patients with previously untreated chronic lymphocytic leukemia; obinutuzumab, in combination with bendamustine followed by obinutuzumab monotherapy, is FDA-approved for treating patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen; and in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for treating adult patients with previously untreated stage II bulky, III or IV follicular lymphoma; obinutuzumab, in combination with chemotherapy followed by obinutuzumab maintenance therapy in patients achieving a response, is EMA-approved for treating patients with previously untreated advanced follicular lymphoma; and in combination with bendamustine followed by obinutuzumab maintenance, in patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.
obinutuzumab/ venetoclax	***TP53*** p.R248Q g.7674220C>T	Sensitive	Venetoclax, a BCL-2 inhibitor, in combination with obinutuzumab, a CD20-directed cytolytic antibody, is EMA-approved for the treatment of adult patients

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Tier 2C **Pathogenic**		with previously untreated chronic lymphocytic leukaemia (CLL).
ofatumumab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Ofatumumab, a CD20-directed cytolytic monoclonal antibody, is FDA- and EMA-approved for treating patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil for whom fludarabine-based therapy is considered inappropriate, patients with relapsed chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide, chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab, and ofatumumab is also FDA-approved as extended treatment in patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive chronic lymphocytic leukemia.
rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy; rituximab is FDA-approved for treating adult patients with relapsed or refractory, low grade or follicular, CD20-positive B cell Non-Hodgkin's Lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens; and previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rituximab is EMA-approved for treating adult patients with previously untreated stage III-IV follicular lymphoma in combination with chemotherapy; follicular lymphoma (maintenance therapy) responding to induction therapy; stage III-IV follicular lymphoma who are chemo-resistant or are

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			in their second or subsequent relapse after chemotherapy; CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy; and for treating patients with previously untreated and relapsed /refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.
rituximab	***TP53*** p.R248Q g.7674220C>T **Tier 2C** Pathogenic	Resistance	Rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy; rituximab is FDA-approved for treating adult patients with relapsed or refractory, low grade or follicular, CD20-positive B cell Non-Hodgkin's Lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens; and previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rituximab is EMA-approved for treating adult patients with previously untreated stage III-IV follicular lymphoma in combination with chemotherapy; follicular lymphoma (maintenance therapy) responding to induction therapy; stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy; CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy; and for treating patients with previously untreated and relapsed /refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
rituximab/ venetoclax	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Venetoclax, a BCL-2 inhibitor, in combination with rituximab, a CD20-directed cytolytic antibody, is EMA-approved for treating adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
venetoclax	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Venetoclax, a BCL-2 inhibitor, is FDA-approved for treating adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); and, in combination with azacitidine or decitabine or low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy; venetoclax, in combination with obinutuzumab, is EMA-approved for treating adult patients with previously untreated CLL; in combination with rituximab, for treating adult patients with CLL who have received at least one prior therapy; and as monotherapy for treating adult patients with CLL in the presence of 17p deletion or TP53 mutation who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or TP53 mutation, for patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
zanubrutinib	***TP53*** p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	Sensitive	Zanubrutinib, a kinase inhibitor, is FDA-approved for treating adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy; and Waldenström's macroglobulinemia (WM).
afatinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3 Uncertain Significance** ***ERBB3*** p.R1127H g.56101239G>A **Tier 3 Uncertain Significance**	Sensitive	Afatinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test, as first-line treatment; metastatic, squamous NSCLC progressing after platinum-based chemotherapy; afatinib is EMA-approved for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation (s) who are EGFR TKI-naïve; and locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum based chemotherapy.
bosutinib	***ERBB2*** p.V116M g.39708441G>A	Sensitive	Bosutinib, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with Philadelphia chromosome-positive chronic

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Tier 3 Uncertain Significance ***ERBB3*** p.R1127H g.56101239G>A **Tier 3 Uncertain Significance**		myelogenous leukemia in chronic, accelerated and blast phases with resistance or intolerance to prior therapy, and newly-diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase.
dacomitinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3 Uncertain Significance** ***ERBB3*** p.R1127H g.56101239G>A **Tier 3 Uncertain Significance**	Sensitive	Dacomitinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.
erlotinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3 Uncertain Significance**	Sensitive	Erlotinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen; and for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine; erlotinib is EMA-approved for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations for the first-line treatment; locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease for switch maintenance treatment after first-line chemotherapy; locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (in patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable); and metastatic pancreatic cancer, in combination with gemcitabine.

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
lapatinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Lapatinib, a kinase inhibitor, in combination with capecitabine, is FDA- and EMA-approved for treating patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab; in combination with letrozole for treating postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated; lapatinib, in combination with trastuzumab, is EMA-approved for treating patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy.
margetuximab	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Margetuximab-cmkb, a HER2/neu receptor antagonist, in combination with chemotherapy, is FDA-approved for treating adult patients with metastatic HER2--positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.
mobocertinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Mobocertinib, a kinase inhibitor, is FDA-approved for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
neratinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance** ***ERBB3*** p.R1127H g.56101239G>A **Tier 3** **Uncertain Significance**	Sensitive	Neratinib, a kinase inhibitor, is FDA-approved as a single agent for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy; and, in combination with capecitabine, for treating adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting; neratinib is EMA-approved for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.
osimertinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3**	Sensitive	Osimertinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Uncertain Significance ***ERBB3*** p.R1127H g.56101239G>A **Tier 3** **Uncertain Significance**		mutations, as detected by an FDA-approved test; osimertinib is FDA-approved for treating adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, as adjuvant therapy after tumor resection; and metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy; osimertinib is EMA-approved for treating adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as adjuvant treatment after complete tumour resection; and locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
pertuzumab	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Pertuzumab, a HER2/neu receptor antagonist, in combination with trastuzumab and docetaxel, is FDA- and EMA-approved for treating patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; in combination with trastuzumab and chemotherapy, for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer; and in combination with trastuzumab and chemotherapy, for adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence; pertuzumab, in combination with trastuzumab and docetaxel, is EMA-approved for treating adult patients with HER2-positive locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
trastuzumab emtansine	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Trastuzumab emtansine, a HER2-targeted antibody and microtubule inhibitor conjugate, is FDA- and EMA-approved for treating patients with HER2-positive metastatic breast cancer as detected by an FDA-approved companion diagnostic who previously received trastuzumab and a taxane, separately or in combination (patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy); trastuzumab emtansine is also FDA-approved for the adjuvant treatment of patients with HER2-positive early breast cancer as detected by an FDA-approved

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			companion diagnostic who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
tucatinib	***ERBB2*** p.V116M g.39708441G>A **Tier 3** **Uncertain Significance**	Sensitive	Tucatinib, a kinase inhibitor, in combination with trastuzumab and capecitabine, is FDA-approved for treating adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting; tucatinib, in combination with trastuzumab and capecitabine, is EMA-approved for treating adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.
erdafitinib	***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Erdafitinib, a kinase inhibitor, is FDA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations as detected by an FDA-approved companion diagnostic and progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.
futibatinib	***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Futibatinib, a kinase inhibitor, is FDA-approved for treating adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.
infigratinib	***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Infigratinib, a kinase inhibitor, is FDA-approved for treating adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.
lenvatinib	***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Lenvatinib, a kinase inhibitor, is FDA- and EMA-approved for treating patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer; in combination with everolimus for treating patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy; and for the first-line treatment of patients with unresectable hepatocellular carcinoma; lenvatinib, in combination with pembrolizumab, is FDA-approved for treating

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
			patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; and in combination with pembrolizumab, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
ponatinib	***FGFR4*** p.N624T g.177096106A>C **Tier 3** **Uncertain Significance**	Sensitive	Ponatinib, a kinase inhibitor, is FDA-approved for treating adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated; T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL; ponatinib is EMA-approved for treating adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation; and adult patients with Ph+ ALL who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.
ruxolitinib	***JAK3*** p.R887H g.17832539C>T **Tier 3** **Uncertain Significance**	Sensitive	Ruxolitinib, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis; and polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea; ruxolitinib is also FDA-approved for treating adult and pediatric patients 12 years and older with steroid-refractory acute graft-versus-host disease.

Available Clinical Trials

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
MS-stable **Tier 2C**	A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability,	pembrolizumab camidanlumab tesirine	Phase 1	United States: CA, CT, OR, TN, TX ADC Therapeutics;

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
Uncertain Significance	Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors NCT03621982			clinical.trials@adctherapeutics.com; 954-903-7994;
MS-stable **Tier 2C Uncertain Significance**	A Phase 1 Open Label, Multi-Arm, Multicenter Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab for Participants With Advanced Solid Tumors NCT03564691	carboplatin MK-4830 lenvatinib pembrolizumab pemetrexed	Phase 1	United States: MO, NJ, NY, TX, UT, WA Toll Free Number; Trialsites@merck.com; 1-888-577-8839;
MS-stable **Tier 2C Uncertain Significance**	A Phase 1A/B Study to Evaluate the Safety and Tolerability of ETC-1922159 as a Single Agent and in Combination With Pembrolizumab in Advanced Solid Tumours NCT02521844	pembrolizumab ETC-1922159	Phase 1	United States: CO, NC, TX Venkateshan Srirangam Prativadibhayankara, MD; Venkateshan_Srirangam@eddc.a-star.edu.sg; +65 6407 4213;
MS-stable **Tier 2C Uncertain Significance**	A Phase 1b/2, Open-Label, Safety, Tolerability and Efficacy Study of NC410 Plus Pembrolizumab for Participants With Advanced Unresectable and/or Metastatic Immune Checkpoint Inhibitor (ICI) Refractory Solid Tumors or ICI Naïve MSS/MSI-Low Solid Tumors NCT05572684	pembrolizumab	Phase 1 /Phase 2	United States: NJ, TX Associate Director Clinical Operations at NextCure, Inc.; NCClin@nextcure.com; 859-468-8632;
MS-stable **Tier 2C Uncertain Significance**	A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (MPH313) Administered in Combination With Nivolumab to Subjects With Locally Advanced or Metastatic Solid Tumors (ACTIVATE) NCT04761198	etigilimab nivolumab	Phase 1 /Phase 2	United States: AZ, CA, FL, MA, MI, MN, NC, NY, OK, TN, TX, UT, VA Bill Feely; enquiries@mereobiopharma.com; 1 650 995 8200;
MS-stable **Tier 2C Uncertain Significance**	A Phase 1/2 Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions NCT03947385	binimetinib LXS196	Phase 1 /Phase 2	United States: AZ, CA, FL, MO, NC, NY, OH, PA, TN, TX IDEAYA Clinical Trials; IDEAYAClinicalTrials@ideayabio.com; +1 650 534 3616;

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
CDKN2A p.H83Y g.21971112G>A **Tier 2C** **Pathogenic**	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial NCT03297606	palbociclib	Phase 2	10 location worldwide Janet Dancey; jdancey@ctg.queensu.ca; 613-533-6430;
CDKN2A p.H83Y g.21971112G>A **Tier 2C** **Pathogenic**	Targeted Agent and Profiling Utilization Registry (TAPUR) Study NCT02693535	palbociclib abemaciclib	Phase 2	United States: AL, AZ, CA, CT, FL, GA, HI, IL, IN, ME, MI, NC, ND, NE, NH, NM, NY, OH, OR, PA, SC, SD, TN, TX, UT, VA, WA, WI John M Lybarger, MPH; john.lybarger@asco.org;
KRAS p.G12A g.25245350C>G **Tier 2C** **Pathogenic**	Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects With Advanced Solid Tumors Harboring Specific Mutations in KRAS NCT05379985	RMC-6236	Phase 1	United States: MA, NY, OH, TN, TX, UT, VA Revolution Medicines, Inc.; rmc-6236_ct-inquiry@revmed.com; (650) 779-2300;
MRE11 p.P230L g.94471730G>A **Tier 2C** **Likely Pathogenic**	Niraparib Plus Carboplatin in Patients With Homologous Recombination Deficient Advanced Solid Tumor Malignancies NCT03209401	carboplatin niraparib	Phase 1	United States: DC, NC, NJ See clinicaltrials.gov for contact information.
MRE11 p.P230L g.94471730G>A **Tier 2C** **Likely Pathogenic**	A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response NCT04550494	talazoparib	Phase 2	United States: FL, MD, OK See clinicaltrials.gov for contact information.
RNF43 p.C272fs*143 g.58360807_58360819delACAGATGGCACAC **Tier 2C** **Likely Pathogenic**	A Phase 1 Open-label Dose Escalation Study of CGX1321 in Subjects With Advanced Solid Tumors With Expansion in Advanced Gastrointestinal Tumors and Phase 1b Study of CGX1321 in Combination With Pembrolizumab in Subjects With Advanced Colorectal Cancer or in Combination With Encorafenib + Cetuximab in Subjects With BRAFV600E Mutated Advanced	cetuximab CGX1321 encorafenib	Phase 1	United States: DC, MA, MD, NC, TX, WI Laurie Rosenstein; rosensteinl@us.curegenix.com;

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
	Colorectal Cancer NCT02675946			
TP53 p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	A Phase Ia/Ib, Open Label, Dose-escalation Study of the Combination of BI 907828 With BI 754091 (Ezabenlimab) and BI 754111 and the Combination of BI 907828 With BI 754091(Ezabenlimab) Followed by Expansion Cohorts, in Patients With Advanced Solid Tumors NCT03964233	miptenalimab BI 907828 ezabenlimab	Phase 1	United States: CT, NY, TX Boehringer Ingelheim; clintriage.rdg@boehringer-ingelheim.com; 1-800-243-0127;
TP53 p.R248Q g.7674220C>T **Tier 2C** **Pathogenic**	A Phase 2 Single-Arm Study of M6620 in Combination With Irinotecan in Patients With Progressive TP53 Mutant Gastric and Gastro-Esophageal Junction Cancer NCT03641313	irinotecan berzosertib	Phase 2	United States: CA, FL, IL, KS, MO, NC, OH, OK, TN, UT See clinicaltrials.gov for contact information.

Individual Variant Interpretations

Biomarker ***TMB-low***
Classification **Tier 2C**
Assessment **Uncertain Significance**

Interpretation
No information available

Biomarker ***MS-stable***
Classification **Tier 2C**
Assessment **Uncertain Significance**

Interpretation
No information available

Gene ***CDKN2A***
Exon 2
Nucleotide NM_000077.5:
g.21971112G>A
c.247C>T
Amino Acid p.H83Y
Function loss
Allelic Fraction 9.22% (of 206 reads)
Classification **Tier 2C**
Assessment **Pathogenic**

Interpretation
The CDKN2A gene encodes multiple proteins, including the tumor suppressor p16INK4a (also known as Mts1), which plays a vital role in cell cycle G1 checkpoint regulation and is an inhibitor of Cdk4 activity. CDKN2A also encodes p14ARF, which regulates p53 by interacting with Mdm2 [278, 232, 279]. Because the CDKN2A and CDKN2B gene products encode proteins that act as tumor suppressors, deletion or loss of activity may result in deregulation of the p16INK4a/Cdk4/Cyclin/Rb and/or the Mdm2/p53 pathways, and altered regulation of the cell cycle [72, 279].

Gene ***KRAS***
Exon 2
Nucleotide NM_004985.5:
g.25245350C>G
c.35G>C
Amino Acid p.G12A
Function gain
Allelic Fraction 39.0% (of 160 reads)
Classification **Tier 2C**
Assessment **Pathogenic**

Interpretation
KRAS is an oncogene that encodes K-Ras, a member of the Ras family of membrane proteins that bind GDP/GTP and possess GTPase activity. Activation of Ras signaling causes cell growth, differentiation, and survival by activating the Raf/MEK/ERK kinase pathway and the PI3K/Akt pathway [191, 115]. The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers [65, 84, 64].

Gene	***MRE11***
Exon	8
Nucleotide	NM_005591.4: g.94471730G>A c.689C>T
Amino Acid	p.P230L
Function	loss
Allelic Fraction	50.0% (of 229 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
MRE11 encodes the protein, meiotic recombination 11 homolog A (Mre11A), which has 3'-5' exonuclease activity and endonuclease activity. As part of the MRN complex with RAD50 and NBS1, Mre11A plays an important role in the DNA damage response, cell cycle checkpoint control, and double-strand DNA break repair [203, 218, 182]. Loss of Mre11 function has been associated with loss of cell cycle checkpoint control and defective DNA damage repair in various tumors; therefore, Mre11A likely acts as a tumor suppressor [23, 258, 180, 149]. Mre11A interacts with Mlh1; Mre11A deficiency has been associated with microsatellite instability in gastrointestinal tumors and colorectal cancer cells [77, 76, 176, 251, 12].

Gene	***POLE***
Exon	34
Nucleotide	NM_006231.4: g.132643513_132643514delCA c.4337_4338delTG
Amino Acid	p.V1446fs*3
Function	loss
Allelic Fraction	2.88% (of 139 reads)
Classification	**Tier 2C**
Assessment	**Pathogenic**

Interpretation
POLE encodes the catalytic subunit of DNA polymerase epsilon complex, which consists of four subunits (POLE, POLE2, POLE3 and POLE4), and is involved in DNA replication and repair [135, 205, 189]. Studies have reported that certain mutations in POLE, including mutations that can compromise the proofreading function of the encoded protein or impair DNA mismatch repair, can lead to an overall increase in genomic mutations that promote cancer formation [4, 267, 117]. Additionally, somatic POLE alterations have been associated with colorectal and endometrial cancer, and germline POLE alterations have been reported in the affected members of families with colorectal, endometrial, ovarian, and brain cancer [35, 178, 43, 202, 93].

Gene	***RNF43***
Exon	7
Nucleotide	NM_001305544.2: g.58360807_58360819delACAGATGGCACAC c.813_825delGTGTGCCATCTGT
Amino Acid	p.C272fs*143
Function	loss
Allelic Fraction	7.71% (of 441 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
RNF43 encodes the protein Rnf43, a tumor suppressor which regulates cell growth and differentiation. Rnf43 functions as an E3 ubiquitin ligase targeting frizzled receptors for degradation and reducing activation of the Wnt/beta-catenin signaling pathway [124, 243, 204]. In the absence of Rnf43, frizzled receptors are stabilized and accumulate on the cell membrane leading to increased sensitivity to Wnt ligand stimulation, activation of the Wnt/beta-catenin signaling pathway, and increased cellular proliferation [124, 111].

Gene	***TP53***
Exon	7
Nucleotide	NM_000546.6: g.7674220C>T c.743G>A
Amino Acid	p.R248Q
Function	gain
Allelic Fraction	8.13% (of 246 reads)
Classification	**Tier 2C**
Assessment	**Pathogenic**

Interpretation
The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the cellular gatekeeper [133]. Loss of p53 is common in aggressive advanced cancers [29]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [208, 145, 231]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [123, 118, 255, 170, 98].

Gene	***AMER1***

Interpretation

Exon 2 Nucleotide NM_152424.4: g.64191641C>T c.1646G>A Amino Acid p.R549Q Function normal Allelic Fraction 6.43% (of 311 reads) Classification **Tier 3** Assessment **Uncertain Significance**	AMER1, also known as WTX or FAM123B, encodes the APC membrane recruitment protein 1, Amer1, which is involved in the regulation of Wnt signaling by recruiting various Wnt pathway modulators, including Apc, Axin, and Gsk3-beta, to the plasma membrane [143, 81, 200, 235, 236, 196]. Amer1 has also been reported to play a role in the nucleus, interacting with Wt1 and enhancing its transcriptional activity [200]. Germline AMER1 inactivation has been associated with osteopathia striata and cranial sclerosis (OSCS) [109, 113, 185, 184, 95, 96, 284]. AMER1 has been described as a tumor suppressor gene frequently inactivated in Wilms tumor samples; recurrent AMER1 mutations have also been reported in colorectal carcinoma and ovarian carcinoma [199, 257, 211, 100, 210, 63].
Gene ***CRLF2*** Exon 3 Nucleotide NM_001012288.3: g.1202520G>A c.29C>T Amino Acid p.P10L Function loss Allelic Fraction 43.0% (of 326 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** CRLF2 (also known as IL-XR and TSLPR) encodes the cytokine receptor subunit Crlf2 that heterodimerizes with IL-7Ralpha to form thymic stromal lymphopoietin (TSLP) receptor [179, 277, 193, 241, 285]. TSLP is a regulator of the inflammatory response and activation of this receptor is associated with allergic reactions [229, 164, 224, 71]. Crlf2, in complex with IL-7Ralpha, has been reported to signal through Jak1, Jak2, Stat3, and Stat5 to promote cell proliferation and inhibit apoptosis [104, 110, 175, 287]. Additionally, activating CRLF2 alterations, often as rearrangements involving IGH or P2RY8, have been associated with activating JAK mutations and B-cell acute lymphoblastic leukemia (B-ALL) [157, 86, 85, 201].
Gene ***EPCAM*** Exon 2 Nucleotide NM_002354.3: g.47373479C>G c.93C>G Amino Acid p.N31K Function normal Allelic Fraction 36.0% (of 163 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** EPCAM encodes the Epithelial cell adhesion molecule, or EpCAM (CDC326), a type 1 transmembrane glycoprotein that is involved in cell-cell adhesion, cell signaling, proliferation, differentiation, and migration [9, 159, 142, 163, 140, 137]. EpCAM protein has been reported to be expressed in most carcinomas, and has been suggested as a tumor marker and a potential tumor target [9, 137]. Many studies have reported that EpCAM plays a role in several cellular processes in cancer, including cellular proliferation, metabolism, migration, and invasion [159, 173, 160, 8]. However, the role of EpCAM in cancer is complex; EpCAM expression has been reported to block metastasis and loss of EpCAM has been associated with aggressive disease stage in some cancer types [228, 121, 209, 14].
Gene ***ERBB2*** Exon 3 Nucleotide NM_004448.4: g.39708441G>A c.346G>A Amino Acid p.V116M Function loss Allelic Fraction 47.0% (of 459 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, which functions as an oncogene, and belongs to the same family as Egfr. Amplification, mutation, and overexpression of ERBB2 can lead to excessive proliferation and tumor formation, and has been reported to play a role in several types of cancer [92, 90]. Activating alterations in the ERBB2 gene or Her2 overexpression may predict sensitivity to Her2 inhibitors [151, 240, 37, 10]. ERBB2 alterations are reported to be mutually exclusive with EGFR and KRAS mutations in non-small cell lung cancer [33, 219]. Exon 20 insertions in ERBB2, resulting in ERBB2 activation, are more common in never smokers in non-small cell lung cancer compared to smokers [219, 33, 7].
Gene ***ERBB3*** Exon 27	**Interpretation** ERBB3 encodes ErbB3 (also known as Her3), a member of the epidermal

Nucleotide	NM_001982.4: g.56101239G>A c.3380G>A
Amino Acid	p.R1127H
Function	normal
Allelic Fraction	48.0% (of 629 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

growth factor receptor (Egfr) family. ErbB3 heterodimerizes with other ErbB receptor tyrosine kinases to transduce growth and survival signals by activating signaling through the Ras/Raf/MAPK and PI3K pathways [217, 276, 242]. Amplification or activating mutations in ERBB3, and ErbB3 heterodimerization with Her2, has been reported to play a role in cell growth and proliferation in several types of cancer [94, 132, 265, 217].

Gene	***ERCC5***
Exon	9
Nucleotide	NM_000123.4: g.102865820A>G c.2108A>G
Amino Acid	p.D703G
Function	normal
Allelic Fraction	48.0% (of 238 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
ERCC5 encodes the ERCC-5 protein (or XPG) that is involved in nucleotide excision repair pathways responsible for repairing UV-induced DNA damage; ERCC-5 specifically functions as an endonuclease mediating the 3' incision and can interact with the transcription factor IIH complex (TFIIH) [214, 215, 105]. ERCC5 plays a critical role in mediating DNA damage repair, which in turn can protect against diseases such as cancer. One study of three cancer cell lines reported that the expression level of ERCC5 was correlated with the extent of nucleotide excision repair activity [122, 214, 146]. Alterations that disrupt the function of ERCC5 have been associated with the development of genetic disorders, including Cockayne's syndrome and xeroderma pigmentosum, the latter of which results in an increased risk of skin cancer [286, 238].

Gene	***FAT1***
Exon	3
Nucleotide	NM_005245.4: g.186663542C>T c.3337G>A
Amino Acid	p.D1113N
Function	loss
Allelic Fraction	38.0% (of 219 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
The FAT1 cadherin gene, encoding Fat1, has been implicated as a negative regulator of Wnt signaling by inhibiting beta-catenin nuclear localization and transcriptional activity [97, 155]. Fat1 activity has been identified at cell-cell interfaces, at distal points of filopodial and lamellipodial structures, and in relation to cellular polarization, with these activities particularly evident during embryogenesis [188, 45, 237, 57, 226]. Fat1 has been characterized in preclinical studies as a tumor suppressor that disrupts Wnt pathway signaling and reduces cell proliferation, growth, migration, and invasion [165, 131, 155]. However, Fat1 has also exhibited characteristics of an oncogene in some cancer types [54, 246].

Gene	***FGFR4***
Exon	14
Nucleotide	NM_213647.3: g.177096106A>C c.1871A>C
Amino Acid	p.N624T
Function	normal
Allelic Fraction	48.0% (of 145 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
FGFR4 encodes Fibroblast growth factor receptor 4 (Fgfr4), a receptor tyrosine kinase that plays a role in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and Akt signaling pathways [190, 245]. FGFR4 mRNA and Fgfr4 protein are overexpressed in several cancer types, and have been shown to play a role in the tumorigenesis of some cancers, including hepatocellular carcinoma and colorectal cancer [68, 183, 138, 244, 264].

Gene	***FUBP1***
Exon	9
Nucleotide	NM_003902.5: g.77964872G>C c.733C>G
Amino Acid	p.Q245E
Function	loss
Allelic Fraction	52.0% (of 221 reads)

Interpretation
FUBP1 encodes far upstream element-binding protein 1, Fubp1, a single-stranded DNA binding protein involved in transcriptional regulation, in particular of the MYC oncogene [87, 27, 275, 58]. In addition, Fubp1 has been reported to bind to RNA and play a role in regulating translation and splicing of several mRNAs, including CDKN1B, NPM, and MDM2 [169, 282, 134, 106]. Fubp1 is overexpressed in a number of cancer types, including hepatocellular carcinoma and non-small cell lung carcinoma,

Classification **Tier 3** Assessment **Uncertain Significance**	and has been reported to play a role in tumor cell proliferation [256, 223, 192, 275, 266]. However, FUPB1 has also exhibited characteristics of a tumor suppressor in oligodendroglioma, indicating that its role in cancer may be context dependent [19, 206, 102, 39, 15].
Gene ***HLA-A*** Exon 3 Nucleotide NM_002116.8: g.29943462_29943463delTTinsCA c.538_539delTTinsCA Amino Acid p.L180Q Function loss Allelic Fraction 100.0% (of 63 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** HLA-A encodes the HLA class I histocompatibility antigen, A alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-A by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 40, 36, 148, 69, 38, 70, 167].
Gene ***HLA-A*** Exon 3 Nucleotide NM_002116.8: g.29943483_29943484delACinsCG c.559_560delACinsCG Amino Acid p.T187R Function normal Allelic Fraction 54.0% (of 119 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** HLA-A encodes the HLA class I histocompatibility antigen, A alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-A by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 40, 36, 148, 69, 38, 70, 167].
Gene ***HLA-A*** Exon 3 Nucleotide NM_002116.8: g.29943494_29943495delGTinsCG c.570_571delGTinsCG Amino Acid p.E190_W191delinsDG Function loss Allelic Fraction 45.0% (of 152 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** HLA-A encodes the HLA class I histocompatibility antigen, A alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-A by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 40, 36, 148, 69, 38, 70, 167].
Gene ***HLA-A*** Exon 5 Nucleotide NM_002116.8: g.29944503_29944504delTGinsCA c.899_900delTGinsCA Amino Acid p.L300P Function gain Allelic Fraction 51.0% (of 45 reads)	**Interpretation** HLA-A encodes the HLA class I histocompatibility antigen, A alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-A by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 40, 36, 148, 69, 38, 70, 167].

Classification	**Tier 3**
Assessment	**Uncertain Significance**

Gene	***HLA-B***
Exon	3
Nucleotide	NM_005514.8: g.31356366_31356367delGTinsTA c.419_420delACinsTA
Amino Acid	p.Y140L
Function	loss
Allelic Fraction	48.0% (of 23 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-B***
Exon	3
Nucleotide	NM_005514.8: g.31356423_31356424delGCinsCG c.362_363delGCinsCG
Amino Acid	p.S121T
Function	normal
Allelic Fraction	86.0% (of 36 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-B***
Exon	3
Nucleotide	NM_005514.8: g.31356429_31356432delGAGGinsCCAA c.354_357delCCTCinsTTGG
Amino Acid	p.L119W
Function	loss
Allelic Fraction	81.0% (of 43 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-B***
Exon	2
Nucleotide	NM_005514.8: g.31356717_31356718delAGinsGC c.313_314delCTinsGC
Amino Acid	p.L105A
Function	loss
Allelic Fraction	98.0% (of 134 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-B***
Exon	2
Nucleotide	NM_005514.8: g.31356748_31356749delCCinsTG c.282_283delGGinsCA
Amino Acid	p.Q94_A95delinsHT
Function	loss
Allelic Fraction	100.0% (of 44 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-B***
Exon	2
Nucleotide	NM_005514.8: g.31356825_31356827delTCTinsGTC c.204_206delAGAinsGAC
Amino Acid	p.E69T
Function	loss
Allelic Fraction	70.0% (of 10 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-B encodes the HLA class I histocompatibility antigen, B alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, antigen presentation, and protective immunity [161, 52, 119]. Inactivation of HLA-B by mutation or genomic deletion has been reported in several cancer types, and has been associated with increased tumor mutational burden [51, 222, 148, 128, 69, 38, 167].

Gene	***HLA-C***
Exon	5
Nucleotide	NM_002117.6: g.31269996_31269997delTGinsCC c.984_985delCAinsGG
Amino Acid	p.T329A
Function	gain
Allelic Fraction	100.0% (of 181 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-C encodes the HLA class I histocompatibility antigen, C alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, NK cell responsiveness, and protective immunity [22, 161, 52, 119, 112]. Downregulation of HLA-C has been reported in leukemia, and specific HLA-C alleles have been identified as protective in cancer development [254, 32, 249, 147, 22, 197, 11].

Gene	***HLA-C***
Exon	4
Nucleotide	NM_002117.6: g.31270232_31270233delTTinsCG c.872_873delAAinsCG
Amino Acid	p.Q291P
Function	gain
Allelic Fraction	97.0% (of 35 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
HLA-C encodes the HLA class I histocompatibility antigen, C alpha chain, a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, NK cell responsiveness, and protective immunity [22, 161, 52, 119, 112]. Downregulation of HLA-C has been reported in leukemia, and specific HLA-C alleles have been identified as protective in cancer development [254, 32, 249, 147, 22, 197, 11].

Gene	***HLA-C***
Exon	3

Interpretation
HLA-C encodes the HLA class I histocompatibility antigen, C alpha chain,

Nucleotide	NM_002117.6: g.31271132_31271133delGTinsAG c.559_560delACinsCT
Amino Acid	p.T187L
Function	loss
Allelic Fraction	32.0% (of 236 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

a classical, highly polymorphic, and essential component of the major histocompatibility Class 1 complex (MHC-1) involved in immune surveillance, NK cell responsiveness, and protective immunity [22, 161, 52, 119, 112]. Downregulation of HLA-C has been reported in leukemia, and specific HLA-C alleles have been identified as protective in cancer development [254, 32, 249, 147, 22, 197, 11].

Gene	***JAK3***
Exon	19
Nucleotide	NM_000215.4: g.17832539C>T c.2660G>A
Amino Acid	p.R887H
Function	loss
Allelic Fraction	58.0% (of 262 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
JAK3 (Janus kinase 3) encodes the Jak3 protein, a tyrosine kinase that regulates signals triggered by cytokines and growth factors, such as erythropoietin, interleukins, and GM-CSF [108]. JAK3 mutations in cancer are typically activating, but loss-of-function mutations have been reported in transient myeloproliferative disorder and acute megakaryoblastic leukemia associated with Down syndrome [49, 144, 260, 78]. Janus-family kinases, including Jak3, activate signal transducer and activator of transcription 3 (Stat3), and persistent Stat3 activation has been reported to play a role in tumor cell proliferation, survival, and invasion [26, 88, 271, 272, 221].

Gene	***KMT2C***
Exon	14
Nucleotide	NM_170606.3: g.152247975G>A c.2459C>T
Amino Acid	p.T820I
Function	loss
Allelic Fraction	13.0% (of 528 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
KMT2C encodes Histone-lysine N-methyltransferase 2C, also called MLL-3, an enzyme that is part of a transcriptional coactivator complex, and is involved in the modification of histones and the positive regulation of transcription [6, 130, 21]. MLL3 is reported to be a tumor suppressor which is involved in a number of cellular processes, including regulation of homeostasis and hormone receptor signaling [6, 21, 120]. Inactivating mutations in MLL3 and downregulation of MLL-3 protein expression have been reported in a number of tumor types and found to play a role in tumorigenesis and leukemogenesis [273, 171, 116, 129, 41, 261].

Gene	***KMT2C***
Exon	14
Nucleotide	NM_170606.3: g.152248143G>A c.2291C>T
Amino Acid	p.S764F
Function	normal
Allelic Fraction	7.33% (of 232 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
KMT2C encodes Histone-lysine N-methyltransferase 2C, also called MLL-3, an enzyme that is part of a transcriptional coactivator complex, and is involved in the modification of histones and the positive regulation of transcription [6, 130, 21]. MLL3 is reported to be a tumor suppressor which is involved in a number of cellular processes, including regulation of homeostasis and hormone receptor signaling [6, 21, 120]. Inactivating mutations in MLL3 and downregulation of MLL-3 protein expression have been reported in a number of tumor types and found to play a role in tumorigenesis and leukemogenesis [273, 171, 116, 129, 41, 261].

Gene	***KMT2D***
Exon	11
Nucleotide	NM_003482.4: g.49051995G>T c.1688C>A
Amino Acid	p.T563N
Function	normal
Allelic Fraction	47.0% (of 157 reads)
Classification	**Tier 3**

Interpretation
KMT2D encodes the MLL-2 protein, a member of the MLL family of histone methyltransferases; MLL-2 has been reported to regulate histone 3 lysine 4 tri-methylation (H3K4me3), which is a modification central to the regulation of transcription [101, 91, 220]. MLL2/KMT2D alterations have been reported in a variety of cancer types, and frequently in non-Hodgkin lymphoma and medulloblastoma, in which the identified MLL2/KMT2D

Assessment **Uncertain Significance**	alterations are predominantly inactivating [181, 154, 82]. MLL2/KMT2D loss of function mutations are also the most common genetic cause of the pediatric disorder known as Kabuki syndrome [162, 34].

Gene ***NOTCH3*** Exon 26 Nucleotide NM_000435.3: g.15170769T>A c.4793A>T Amino Acid p.D1598V Function normal Allelic Fraction 53.0% (of 590 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** NOTCH3 encodes Notch3, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [17, 125]. NOTCH3 mutations have been implicated in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) [239, 1]. NOTCH3 has been shown to function as an oncogene or a tumor suppressor, depending on the tumor type or the context [16, 46, 47, 99, 283, 107]. Indeed, upregulation of Notch3 protein has been reported in several tumor types, including prostate carcinoma and T-cell acute lymphoblastic leukemia (T-ALL), while loss of Notch3 expression has been found in medullary thyroid carcinoma [16, 47, 107].

Gene ***PARP1*** Exon 13 Nucleotide NM_001618.4: g.226377176C>T c.1873G>A Amino Acid p.A625T Function normal Allelic Fraction 47.0% (of 147 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** PARP1 encodes poly (ADP-ribose) polymerase 1 (PARP-1), which has a predominant role in base excision repair, as well as in modulation of cell signaling and metabolism [48, 207, 67]. Although PARP-1 may be activated in cancer cells in response to increased DNA damage, PARP-1 also appears to play a role in many other cellular processes, often via transcriptional regulation [166, 126, 48, 207, 28, 150].

Gene ***PRKCI*** Exon 9 Nucleotide NM_002740.6: g.170280374G>A c.853G>A Amino Acid p.V285M Function loss Allelic Fraction 7.26% (of 634 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** PRKCI encodes an atypical protein kinase C, PKC-iota, that plays a critical role in determining cell polarity and has been implicated in mediating resistance to cellular apoptosis [262, 141, 234, 139, 216]. PRKCI has been reported to be an oncogene overexpressed in a wide variety of cancer types; PKC-iota has been reported to play a role in tumor invasion and survival [59, 195, 158, 177].

Gene ***RNF43*** Exon 8 Nucleotide NM_001305544.2: g.58360176A>T c.925T>A Amino Acid p.C309S Function loss Allelic Fraction 11.0% (of 284 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** RNF43 encodes the protein Rnf43, a tumor suppressor which regulates cell growth and differentiation. Rnf43 functions as an E3 ubiquitin ligase targeting frizzled receptors for degradation and reducing activation of the Wnt/beta-catenin signaling pathway [124, 243, 204]. In the absence of Rnf43, frizzled receptors are stabilized and accumulate on the cell membrane leading to increased sensitivity to Wnt ligand stimulation, activation of the Wnt/beta-catenin signaling pathway, and increased cellular proliferation [124, 111].

Gene ***SMC3***	**Interpretation**

Exon	20
Nucleotide	NM_005445.4: g.110598186G>A c.2164G>A
Amino Acid	p.E722K
Function	normal
Allelic Fraction	7.45% (of 470 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

SMC3 encodes Structural maintenance of chromosomes protein 3 (Smc3), a key part of the cohesin complex that maintains chromosome segregation fidelity, contributes to DNA repair and recombination, and participates in microtubule-mediated transport [75, 74, 44, 227]. Loss of Smc3 activity has been associated with chromosomal instability, as well as development of hematopoietic neoplasms in preclinical studies [74, 156, 250].

Gene	***TENT5C***
Exon	2
Nucleotide	NM_017709.4: g.117623222C>A c.354C>A
Amino Acid	p.N118K
Function	normal
Allelic Fraction	45.0% (of 213 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
The interferon-stimulated gene FAM46C (also referred to as TENT5C) encodes Fam46C, a protein that has been implicated in the replication of certain viruses, including yellow fever, west Nile, chikungunya, and Venezuelan equine encephalitis [213]. FAM46C has been identified as one of several super enhancer genes in MYC rearrangements driving expression of Myc in multiple myeloma [2, 252].

Gene	***ZFHX3***
Exon	2
Nucleotide	NM_006885.4: g.72957864C>A c.2282G>T
Amino Acid	p.G761V
Function	loss
Allelic Fraction	49.0% (of 211 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
ZFHX3 encodes zinc finger homeobox protein 3, also called ATBF1 (AT motif-binding factor 1), a transcriptional regulator that modulates numerous processes including hormone signaling, calcium homeostasis, and myoblast differentiation [18, 56, 281, 280, 152]. ATBF1 has been reported to play a tumor suppressor role in numerous cancers [233, 56, 80, 253].

Genes Tested

ABCB9, ABL1, ABL2, ACE2, ACVR1B, AKT1, AKT2, AKT3, ALK, ALPK2, AMER1, APC, AR, ARAF, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L1, BCL6, BCOR, BCORL1, BLM, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTK, CALR, CANX, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD200, CD274, CD276, CD40, CD40LG, CD48, CD70, CD79A, CD79B, CD80, CD86, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHD4, CHEK1, CHEK2, CIC, CNKSR1, COL5A1, CREBBP, CRKL, CRLF2, CSF1R, CTCF, CTNNA1, CTNNB1, CTSB, CTSL, CTSS, CUL3, CUL4B, CUX1, CYLD, DAXX, DDR2, DDX3X, DICER1, DIS3, DMD, DNER, DNMT3A, DOT1L, EED, EGFR, EP300, EPCAM, EPHA3, EPHA5, EPHA7, EPHB1, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ETV6, EWSR1, EXO1, EZH2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FAS, FAT1, FBXW7, FGF19, FGF3, FGF4, FGFBP1, FGFR1, FGFR2, FGFR3, FGFR4, FH, FKBP9, FLCN, FLT1, FLT3, FLT4, FOXA1, FOXL2, FOXP1, FUBP1, GABRA6, GADD45A, GATA1, GATA2, GATA3, GATA4, GATA6, GLI1, GNA11, GNA13, GNAQ, GNAS, GRIN2A, GSK3B, H3-3A, H3C2, HERC1, HGF, HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, HMGB1, HMGN1, HNF1A, HRAS, HSP90AA1, ICOSLG, IDE, IDH1, IDH2, IFI30, IGF1R, IGF2, IGF2R, IKBKE, IKZF1, IL7R, INPP4B, IRF4, IRF6, IRS2, ITGAV, ITGB3, JAK1, JAK2, JAK3, JUN, KAT6A, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KEL, KIT, KMT2A, KMT2C, KMT2D, KRAS, LGALS9, LGMN, LIG1, LIG3, LMO1, LNPEP, LPAR2, LRP1B, LZTR1, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MCL1, MCM2, MCM3, MCM4, MCM5, MCM6, MCM7, MDM2, MDM4, MED12, MEF2B, MEN1, MET, MICA, MICB, MITF, MLH1, MLH3, MORC4, MPL, MR1, MRE11, MSH2, MSH3, MSH4, MSH5, MSH6, MTOR, MUC17, MUTYH, MYB, MYC, MYCL, MYCN, MYD88, MYOCD, NBN, NCOR1, NF1, NF2, NFE2L2, NFKBIA, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPEPPS, NPM1, NRAS, NRDC, NSD1, NTRK1, NTRK2, NTRK3, PALB2, PARP1, PAX5, PBRM1, PCNA, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PDK1, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3CG, PIK3R1, PIK3R2, PIM1, PLCG2, PMS1, PMS2, POLB, POLD1, POLD2, POLD3, POLD4, POLE, POLE4, PPP2R1A,

PRDM1, PRKAR1A, PRKCG, PRKCI, PRKCZ, PRKDC, PRKN, PSMA1, PSMA2, PSMA3, PSMA4, PSMA5, PSMA6, PSMA7, PSMA8, PSMB1, PSMB10, PSMB11, PSMB2, PSMB3, PSMB4, PSMB5, PSMB6, PSMB7, PSMB8, PSMB9, PSMC1, PSMC2, PSMC3, PSMC4, PSMC5, PSMC6, PSMD1, PSMD10, PSMD11, PSMD12, PSMD13, PSMD14, PSMD2, PSMD3, PSMD4, PSMD5, PSMD6, PSMD7, PSMD8, PSMD9, PSME1, PSME2, PSME3, PSME4, PSMF1, PSMG1, PSMG2, PSMG3, PSMG4, PTCH1, PTEN, PTGS2, PTPN11, PTPRD, QKI, RAC1, RAD17, RAD18, RAD21, RAD50, RAD51, RAD51C, RAF1, RARA, RASA1, RB1, RBM10, REL, RET, RFC1, RFC2, RFC3, RFC4, RFC5, RHEB, RHOA, RICTOR, RIT1, RNASEH2A, RNF43, ROS1, RPA1, RPA2, RPA3, RPA4, RPTOR, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SF3B1, SIRT1, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMC1A, SMC3, SMO, SOCS1, SOS1, SOX10, SOX17, SOX2, SOX9, SPEN, SPOP, SRC, SSBP1, STAG2, STAT3, STK11, SUFU, SUZ12, SYK, TAP1, TAP2, TAPBP, TAPBPL, TBX3, TCF7L2, TCP11L2, TDG, TENT5C, TERC, TERT, TET2, TGFBR2, TNF, TNFAIP3, TNFRSF14, TNFRSF9, TNFSF14, TNFSF18, TNFSF4, TNFSF9, TNKS, TOP1, TP53, TP53BP1, TP73, TPP2, TREX1, TRRAP, TSC1, TSC2, TSHR, U2AF1, VEGFA, VEGFD, VHL, VSIR, VTCN1, WEE1, WT1, XPO1, XRCC5, ZFHX3, ZNF217

Methods and Limitations

EXAMPLE Statement including sample type (FFPE, etc), method of extraction, amplification reactions, panel targeted regions, sequencing technology, etc. Additionally, a description of the data analysis software(s), genome of reference and the sensitivity of the methods should be described.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (9.0.0.20220826), Ingenuity Knowledge Base (H-release), CADD (v1.6), NCBI Gene (2022-02-22), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2022-02-22), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2022-11-12 13:22:36.407), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (H-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Jul 13 22:57), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (April 13, 2022), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2022-04-14), DGV (2016-05-15), COSMIC (v95), HGMD (2022.3), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Clinical Significance of Variants Based on AMP / ASCO / CAP Guidelines*

Strong Significance	**Tier 1A**	• Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis • Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	• Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies • Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential Significance	**Tier 2C**	• Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis • Biomarker is an inclusion criterion for an active clinical trial • Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	• Biomarker shows plausible response or resistance based on case or preclinical studies • Biomarker may assist in disease diagnosis or prognosis based on small studies

Uncertain Significance	**Tier 3**	• Biomarker has uncertain clinical significance and not known to be likely benign or benign

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