FOUNDATIONONE®LIQUID CDx

PATIENT
Li, Cheng-Wan

TUMOR TYPE
Ampullary adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
20 March 2023
ORDERED TEST #
ORD-1585611-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Ampullary adenocarcinoma
NAME Li, Cheng-Wan
DATE OF BIRTH 20 May 1951
SEX Male
MEDICAL RECORD # 49323435

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID CWL 5/20/1951
SPECIMEN TYPE Blood
DATE OF COLLECTION 09 March 2023
SPECIMEN RECEIVED 13 March 2023

Biomarker Findings

Blood Tumor Mutational Burden - 10 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ERBB2 D769Y
ATM splice site 3077+1G>A, T656fs*2, Q2714*
CHEK2 T387A
RNF43 Q670*
CREBBP inversion exons 18-19
DNMT3A R882H
TET2 A1355V
TNFAIP3 P425L
U2AF1 S34F

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Ado-trastuzumab emtansine** (p. 13), **Fam-trastuzumab deruxtecan** (p. 14), **Lapatinib** (p. 14), **Neratinib** (p. 15), **Trastuzumab** (p. 15), **Trastuzumab + Pertuzumab** (p. 16)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 17)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***ATM* Q2714*, splice site 3077+1G>A, T656fs*2** (p. 8), ***CHEK2* T387A** (p. 9), ***DNMT3A* R882H** (p. 10), ***TET2* A1355V** (p. 11), ***U2AF1* S34F** (p. 12)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 10 Muts/Mb **10 Trials** see p. 17	None	None
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**	
Tumor Fraction - Elevated Tumor Fraction	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).**	

Electronically signed by Matthew Hiemenz, M.D. | 20 March 2023
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 -	D769Y	6.7%	None	Ado-trastuzumab emtansine Fam-trastuzumab deruxtecan Lapatinib Neratinib Trastuzumab Trastuzumab + Pertuzumab
10 Trials see p. 23				
ATM -	splice site 3077+1G>A	0.73%	None	None
	T656fs*2	0.23%		
	Q2714*	0.17%		
10 Trials see p. 19				
CHEK2 -	T387A	0.25%	None	None
10 Trials see p. 21				
RNF43 -	Q670*	4.0%	None	None
3 Trials see p. 25				

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

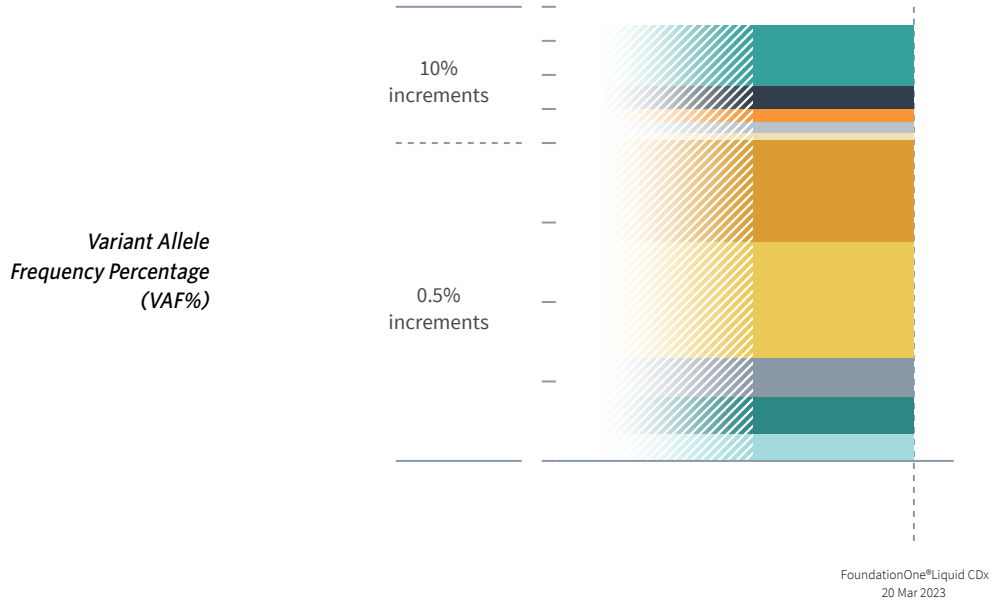
Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1585611-01 VAF%
Blood Tumor Mutational Burden		10 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		10%
ERBB2	● D769Y	6.7%
ATM	● T656fs*2	0.23%
	● splice site 3077+1G>A	0.73%
	● Q2714*	0.17%
CHEK2	● T387A	0.25%
RNF43	● Q670*	4.0%
CREBBP	inversion exons 18-19	2.1%
DNMT3A	● R882H	1.9%
TET2	● A1355V	1.7%
TNFAIP3	● P425L	17.7%

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HISTORIC PATIENT FINDINGS		ORD-1585611-01 VAF%
U2AF1	S34F	3.2%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable or reportable variants may become VUS.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

BIOMARKER

Blood Tumor Mutational Burden

RESULT
10 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (NSCLC), multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single-agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (HNSCC), a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). Hypermutated cases were enriched in a poor prognosis subgroup of patients with biliary tract cancer[12], but the effects of TMB on prognosis of patients with ampullary cancer have not been extensively investigated (PubMed, Sep 2022).

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[13-14] and cigarette smoke in lung cancer[15-16], treatment with temozolomide-based chemotherapy in glioma[17-18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,4].

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[24-29].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[30]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[31], Ewing sarcoma and osteosarcoma[32], prostate cancer[27], breast cancer[33], leiomyosarcoma[34], esophageal cancer[35], colorectal cancer[36], and gastrointestinal cancer[37].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[38], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[39-40].

GENE
ERBB2

ALTERATION
D769Y

TRANSCRIPT ID
NM_004448.2

CODING SEQUENCE EFFECT
2305G>T

VARIANT CHROMOSOMAL POSITION
chr17:37880261

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[41-46], pertuzumab in combination with trastuzumab[43,47-49], and zanidatamab (ZW25)[50], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[51] and fam-trastuzumab deruxtecan (T-DXd)[52-54], HER2 kinase inhibitors such as tucatinib[55-58], and dual EGFR/HER2 kinase inhibitors such as lapatinib[59-67], afatinib[46,68-77], neratinib[78-81], dacomitinib[82], and pyrotinib[83-84] . The Phase I trial of HER2-selective TKI BI-1810631 for patients with HER2-aberration-positive metastatic solid tumors reported a 3.7% ORR (7/19) and an 84% DCR; for patients with NSCLC, a 45% ORR (5/11) and a 91% DCR were reported[85]. A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17% (4/23) for ERBB2-altered solid tumors, with PRs for 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[86]. Patients with ERBB2-mutated non-small cell lung cancer (NSCLC) have also benefited from pyrotinib (30-53% ORR)[87].

FREQUENCY & PROGNOSIS

ERBB2 mutation has been reported in 4% of ampulla of Vater carcinomas[88], 0.5% of pancreatic adenocarcinomas[89], 8% (7/83) of small bowel adenocarcinomas[90], and 2.4% of bile duct carcinomas (COSMIC, Oct 2022)[91]. ERBB2 amplification is more frequent in both ampullary and pancreatic adenocarcinoma, reported in 13-23% of ampulla of Vater carcinomas[92-93] and 6-25% of pancreatic carcinomas[94-96]. In small intestine carcinoma, ERBB2 amplification has been reported in 3-5% (3/83 to 10/184) of cases[90,97]. Several studies have suggested that HER2 expression is an unfavorable prognostic indicator in duodenal adenocarcinoma and ampulla of Vater carcinoma[98-100]. In contrast, one study found that neither overexpression nor amplification of ERBB2 correlated with clinico-pathological features in small intestine carcinoma[97]. In pancreatic adenocarcinoma, ERBB2 amplification was not found to correlate significantly with patient survival in one study[95], but HER2 overexpression was reported to correlate with worse prognosis in other studies[96,101-103].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. ERBB2 mutations, such as observed here, have been shown to be activating[104-114]. Patients with other ERBB2 activating mutations have had clinical responses to regimens that include ERBB2 targeted therapies, including trastuzumab[43-44,46,63,115], pertuzumab[43,63], lapatinib[62-64], afatinib[46,70,116], neratinib[72,78,117], and dacomitinib[82].

GENE

ATM

ALTERATION
splice site 3077+1G>A, T656fs*2, Q2714*

TRANSCRIPT ID
NM_000051.3, NM_000051.3, NM_000051.3

CODING SEQUENCE EFFECT
3077+1G>A, 1967_1968delCT, 8140C>T

VARIANT CHROMOSOMAL POSITION
chr11:108142134, chr11:108124608-108124610, chr11:108205825

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[118-119]. Clinical responses have been reported for patients with ATM-mutated prostate cancer treated with PARP inhibitors[120-122] and PARP inhibitors have shown limited clinical benefit for patients with other ATM-mutated solid tumors including pancreatic cancer[123-124] , colorectal cancer[125], papillary renal cell carcinoma[126], ovarian cancer[127], small cell bowel cancer,[124], and biliary tract cancer[128]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[129] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[130] harbored ATM inactivation or protein loss. In a Phase 2 study of a combination of the ATR inhibitor ceralasertib and durvalumab for patients with advanced gastric cancer, objective responses (ORs) were experienced by 50% (4/8) of patients with loss of ATM expression, compared with 14% (3/21) patients with intact ATM[131]. Studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[132-134] and hematologic malignancies[132,135] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[136].

FREQUENCY & PROGNOSIS

ATM mutations were identified in 2/80 of ampulla of Vater carcinomas in one study[88] and in 1/25 ampullary carcinoma samples in another[137]. ATM mutations have been reported infrequently in cholangiocarcinoma (5%)[138]. ATM alterations have been observed in various solid tumors, with mutations being more frequent than gene loss and often seen in small bowel (7-9%), endometrial (7%), non-melanoma skin (3-6%), bladder (5%), hepatobiliary (4-5%), colorectal (4-5%), and lung (3%) cancer[137,139]. Expression of the ATM protein has been observed in 67.7% of pancreatic tumors, where it was correlated with p53 expression[140]. Some familial mutations in ATM have been suggested to increase the risk of developing pancreatic cancer[141-142]. Published data investigating the prognostic implications of ATM alterations in ampullary adenocarcinoma are limited (PubMed, Jun 2022).

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[143]. Loss of functional ATM promotes tumorigenesis[144]. Alterations such as seen here may disrupt ATM function or expression[145-147]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the ATM variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with ataxia-telangiectasia syndrome (ClinVar, Sep 2022)[148]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[149]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[150]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[143,150]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[150]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[151-156]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[155,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
CHEK2

ALTERATION
T387A

TRANSCRIPT ID
NM_007194.3

CODING SEQUENCE EFFECT
1159A>G

VARIANT CHROMOSOMAL POSITION
chr22:29091798

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors[120-122]. Clinical benefit has been observed for patients with ovarian[159] and testicular[160] cancers treated with PARP inhibitors. In a study of patients with metastatic breast cancer, 8 patients with CHEK2 mutation did not respond to olaparib treatment[161]. One study of patients with breast cancer reported that carriers of the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy[162], whereas another study found that those who carry CHEK2 mutations have a lower frequency of objective clinical responses to neoadjuvant therapy[163]. A third study reported that the CHEK2 1100delC mutation is not associated with differential efficacy of chemotherapy and endocrine therapy in patients with metastatic breast cancer[164].

FREQUENCY & PROGNOSIS

Somatic CHEK2 mutations have been reported in 0-3% of various solid tumors, with the highest incidence reported in prostate, brain, endometrial, urothelial, and skin tumors (COSMIC, Jan 2023)[91]. In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors as well as bilateral disease[165]. A study reported that a polymorphism in CHEK2 was associated with worse survival of patients with GBM, but this association lost significance after adjusting for other prognostic factors[166-167]. Another study in prostate cancer reported that CHEK2 expression is decreased in higher grade tumors and that CHEK2 is a tumor suppressor that decreases the growth of prostate cancer cells and regulates androgen receptor signaling[168].

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor[169-172]. Alterations such as seen here may disrupt CHEK2 function or expression[173-183].

POTENTIAL GERMLINE IMPLICATIONS

Germline CHEK2 mutation has been associated with cancer susceptibility of low to moderate penetrance, especially in hereditary breast cancer[184]. CHEK2 germline mutation has been identified in approximately 2.5% of familial or high-risk breast cancer cases[185-186]. Although heterozygous germline CHEK2 mutation increases breast cancer risk two- to three-fold, it is not associated with younger age at diagnosis[186-187]. In the appropriate clinical context, germline testing of CHEK2 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[151-156]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[155,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
RNF43

ALTERATION
Q670*

TRANSCRIPT ID
NM_017763.4

CODING SEQUENCE EFFECT
2008C>T

VARIANT CHROMOSOMAL POSITION
chr17:56435129

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[188-192]. In a Phase 1 basket study for the Porcupine inhibitor RXC004, 1 of 2 patients with tumors harboring an RNF43 mutation achieved SD[193]. Of the patients with WNT-ligand-dependent tumors, including those with RNF43 mutations, RSPO fusions, or those with biliary tract or thymus cancer, 71% (5/7) experienced SD[193]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[194-195], 3-5% of pancreatic cancers[196], 21% of ovarian mucinous carcinomas[197], 9% of liver fluke-associated cholangiocarcinomas[198], and up to 18% of colorectal cancers[22,195]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[195], endometrial[195], and gastric cancers[199-200]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[199].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[201] that was discovered because it is overexpressed in colon cancer[202]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[188-192]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[203].

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GENE
CREBBP

ALTERATION
inversion exons 18-19

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CREBBP. Limited data suggest that CREBBP mutations may be associated with sensitivity to histone deacetylase inhibitors, although conflicting data have also been reported[204-208].

FREQUENCY & PROGNOSIS

CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 26%) and diffuse large B-cell lymphoma (DLBCL, 16%), and at lower frequency in acute lymphoblastic leukemia (ALL, 7%), and tumors of the urinary tract (15%), skin (12%), liver (8.7%), endometrium (8.5%), and stomach (8.2%)(COSMIC, 2023)[91]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[209], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[210]. Reports have found CREBBP mutation in 62-68% of patients with FL[211-212], which was associated with immune evasion[211]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[213-214].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[215]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[216]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[217-218].

GENE
DNMT3A

ALTERATION
R882H

TRANSCRIPT ID
NM_022552.3

CODING SEQUENCE EFFECT
2645G>A

VARIANT CHROMOSOMAL POSITION
chr2:25457242

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, COSMIC, PubMed, Feb 2023)[91,219-220]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2023).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[221-222]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[223-228]. Mutations at codon 882, including R882S, R882H, and R882C, have demonstrated reduced methyltransferase activity in vitro, with R882H and R882C conferring increased cell proliferation[229-231]. About half of all DNMT3A mutations in AML are R882H, which leads to a partially defective enzyme and altered oligomerization behavior, although the effect on global methylation remains to some extent controversial; in addition, at least one report suggests that mutation of R882 is associated with sensitivity to DNA methyltransferase inhibitors[229-232]. On the basis of this, any alteration at R882 is likely to promote tumorigenesis, although the efficacy of DNMT inhibitors may not be consistent for all mutations.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[151-156]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[151-152]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[233]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[155,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
TET2

ALTERATION
A1355V

TRANSCRIPT ID
NM_001127208.2

CODING SEQUENCE EFFECT
4064C>T

VARIANT CHROMOSOMAL POSITION
chr4:106190786

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies[137]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2023).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[234-235]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL CLONAL HEMATOPOIESIS

IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[151-156]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[151-152]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[233]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[155,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
TNFAIP3

ALTERATION
P425L

TRANSCRIPT ID
NM_006290.2

CODING SEQUENCE EFFECT
1274C>T

VARIANT CHROMOSOMAL POSITION
chr6:138199856

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that address the loss of TNFAIP3. A20 has multiple functions and is subject to a wide range of genomic lesions, thereby making it challenging to develop a unified therapeutic approach. Potential avenues targeting dysregulation of ubiquitination pathways include anti-CD20 therapies, such as rituximab, and proteasome inhibitors, such as bortezomib[236].

RNAi-mediated downregulation of TNFAIP3 has been reported to sensitize multiple myeloma cells to bortezomib[237].

FREQUENCY & PROGNOSIS

In the COSMIC dataset, TNFAIP3 mutations have been reported in 3.4% of prostate, 3.4% of skin, 2.8% of endometrial, and 2.3% of large intestine cancers (2023)[91]. Overexpression of TNFAIP3 has been associated with aggressive high-grade ER-/PR-negative breast tumors[238], resistance to TNF-alpha and TRAIL-induced apoptosis in glioblastoma[239-240] and to chemotherapy in acute lymphoblastic leukemia[241], and poor prognosis in adrenocortical carcinoma[242]. Loss of heterozygosity in the genomic region including TNFAIP3 has been found in 16.8% (25/149) of colorectal adenocarcinomas, and significantly decreased TNFAIP3 mRNA expression has been observed in colorectal cancer (CRC) tumors compared with adjacent non-neoplastic mucosa[243]. Reduced A20 expression has been suggested as a marker of poor prognosis in CRC[244].

FINDING SUMMARY

TNFAIP3 encodes tumor necrosis factor alpha-induced protein 3, also known as A20, a regulator of NF-kB signaling and apoptosis[245] that has both ubiquitin ligase and deubiquitinase activities[246-247] and whose loss or inactivation may be tumorigenic[248]. TNFAIP3 is frequently deleted or mutated in lymphoma, where it functions as a tumor suppressor[248], but its expression and function are context dependent in solid tumors[245,249-252], leukemia[241,253-254], and multiple myeloma[255-256]. TNFAIP3 mutations that disrupt the A20p37 chain (amino acids 371–790), which mediates ubiquitin ligase activity and interaction with the cIAP1/TRAF2 complex[246,257], are predicted to be inactivating. In T-cells, cleavage of A20 codon R439 by MALT1 has been shown to upregulate NFkB signaling; R439A has been shown to block MALT1-mediated NF-kB activation[258]; however, the function of R439 mutations outside of the context of T-cell lymphoma has not been reported.

GENE
U2AF1

ALTERATION
S34F

TRANSCRIPT ID
NM_006758.2

CODING SEQUENCE EFFECT
101C>T

VARIANT CHROMOSOMAL POSITION
chr21:44524456

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies approved or in clinical trials that directly address genomic alterations in U2AF1; however, preclinical studies suggest that mutations in genes encoding spliceosome components, including U2AF1, may confer sensitivity to spliceosome inhibitors[259-263]. In preclinical models, U2AF1 mutation leads to DNA damage and ATR pathway activation, rendering cells sensitive to ATR inhibitors both alone and in combination with spliceosome inhibitors[264-265].

FREQUENCY & PROGNOSIS

Mutations in U2AF1 have been reported in 2.9% of endometrial, 2.6% of peritoneal, 2.2% of small intestine, and less than 2% of other solid tumor types (COSMIC, Aug 2022)[91]. U2AF1 mutations have been associated with significantly shorter survival for patients with lung adenocarcinoma[266].

FINDING SUMMARY

U2AF1 encodes a pre-mRNA splicing factor required for accurate 3' splice site selection[267-268]. The S34F mutation is commonly found in patients with myelodysplastic syndrome (MDS), and is located in the first zinc finger domain of the protein; this alteration has been shown to affect splicing in preclinical cell-based assays[268-269]. This mutation has been reported to be a common mutation in acute myeloid leukemia (AML), accounting for 47% of U2AF1 mutations in AML in one study[270].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[151-156]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[151-152]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[233]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[155,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Ado-trastuzumab emtansine

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[51,271-286] .

SUPPORTING DATA

Clinical data on the efficacy of ado-trastuzumab emtansine (T-DM1) for the treatment of ampullary or small intestine carcinoma are limited (PubMed, Jan 2023); a case study of HER2-targeted therapies reported PD as best response for 1 patient with ampullary carcinoma treated with T-DM1[287]. Phase 2 basket trials of T-DM1 in ERBB2-amplified advanced solid tumors reported an ORR of 0-17% (0/3-1/7) for patients with previously treated biliary tract cancers[271-272] ; the best outcomes were one PR with disease progression after 8.6 months for a patient with extrahepatic cholangiocarcinoma in one study[272,286] and 3 short-term SD (<5 months) outcomes in the other study[271]. The vast majority of data on the therapeutic use of T-DM1 have been collected in the context of breast cancer, although clinical trials investigating T-DM1 are under way in several tumor types, primarily in HER2+ cancers. Phase 2 basket trials for HER2-amplified cancers have reported ORRs of 8-28% with T-DM1, including responses in salivary gland, lung, endometrial, biliary tract, and ovarian cancers[272,279]. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved PFS and a lower rate of adverse events than patients who received the physician's choice of therapy[275]. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer OS and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[51,276] . Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with ORRs of 35% and 26%, respectively, and PFS of 6.9 months and 4.9 months, respectively[277-278] .

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma. It is also approved for patients with HER2-low advanced breast cancer who have previously been treated with chemotherapy, as well as for patients with advanced ERBB2-mutated non-small cell lung cancer (NSCLC) who have received systemic therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[54,288] , ERBB2 missense or exon 20 insertion mutations may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

Clinical data on the efficacy of fam-trastuzumab deruxtecan for the treatment of ampullary adenocarcinoma are limited (PubMed, Mar 2023). A Phase 2 study of fam-trastuzumab deruxtecan (T-DXd) for patients with HER2+ or HER2-low advanced biliary tract cancer reported ORRs of 36% (8/22) and 13% (1/8) and median OS of 7.1 and 8.9 months for the HER2+ and HER2-low cohorts, respectively[289]. Benefit was also observed in a Phase 1 trial of T-DXd with objective responses reported in each of the 2 included patients with HER2+ biliary tract cancer and a patient with pancreatic cancer[288]. Fam-trastuzumab deruxtecan has demonstrated activity in multiple ERBB2-positive cancer types. In the Phase 2 DESTINY trials, clinical benefit was observed for patients treated with fam-trastuzumab deruxtecan monotherapy who had previously treated, HER2-expressing breast (61% ORR, median PFS 16.4 months)[52], colorectal (45% ORR, median PFS 6.9 months)[290], or gastric or gastroesophageal cancer (43% ORR, median PFS 5.6 months)[53], as well as HER2-mutated lung cancer (62% ORR, median PFS 14.0 months)[291]. Benefit was also observed in a Phase 2 trial for ERBB2-expressing biliary tract cancer (30% ORR)[289]. In a Phase 1 study evaluating single-agent fam-trastuzumab deruxtecan for the treatment of patients with ERBB2-mutated solid tumors or ERBB2-expressing solid tumors other than breast or gastric cancer, the median PFS was 7.2 months and the ORR was 28% (17/60), with responses reported for patients with non-small cell lung carcinoma (NSCLC), breast cancer, colorectal cancer (CRC), salivary gland carcinoma, cholangiocarcinoma, and endometrial cancer[288].

Lapatinib

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[59-67] .

SUPPORTING DATA

Clinical data on the efficacy of lapatinib to treat ampullary, duodenal, or small intestine carcinoma are limited (PubMed, Nov 2022). Phase 2 studies have indicated limited activity of single-agent lapatinib for genomically unselected biliary tract cancer[292-293] . A Phase 2 study of lapatinib monotherapy for patients with advanced biliary tract cancer and ≤1 prior chemotherapy regimen reported SD as the best response in 24% (4/17) patients, with a median PFS of 1.8 months and a median OS of 5.2 months[292]; similar results were reported in a smaller Phase 2 study[293]. Phase 1 studies have reported PRs in genomically unselected patients with bile duct carcinoma, gallbladder carcinoma, or cholangiocarcinoma treated with lapatinib plus gemcitabine with or without oxaliplatin[294], or with lapatinib plus FOLFOX4[295].

Neratinib

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[78-81,296-298] and preclinical[105-106,112,299-300] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

Among patients with advanced biliary tract cancer in the Phase 2 SUMMIT basket trial evaluating neratinib in HER2-mutated tumors, treatment resulted in an ORR of 16% (4/25) and clinical benefit rate of 28%, including 4 PRs and 3 SDs ≥16 weeks; median PFS and OS were 2.8 and 5.4 months, respectively. Median PFS for cholangiocarcinoma (1.4 months, n=11), gallbladder (3.7 months, n=10), and ampullary (1.1 months, n=4) cohorts were reported[301]. Neratinib has been largely evaluated in the context of breast cancer and non-small cell lung cancer (NSCLC). For patients with advanced HER2-positive breast cancer, neratinib treatment resulted in PFS of 22.3 weeks for patients with prior trastuzumab treatment and 39.6 weeks for those with no prior trastuzumab treatment[302]. In patients with HER2-positive breast cancer with brain metastases, neratinib elicited a CNS ORR of 8% (3/40)[303]. In a Phase 3 study of patients with HER2-positive, early stage breast cancer previously treated with trastuzumab, neratinib significantly improved the 2-year invasive disease-free survival compared to placebo (HR=0.67, p=0.0091)[297]. In Phase 2 trials of single-agent neratinib for patients with ERBB2-mutated, non-amplified metastatic breast cancer, clinical benefit rates of 31-40% and median PFS of 3.5-4 months have been achieved[79-81] . Neratinib in combination with various other agents has also shown significant clinical activity against breast cancer[298,304-309] . In patients with ERBB2-mutated NSCLC, where the majority of cases harbor inhibitor-resistant exon 20 insertions, neratinib monotherapy has resulted in ORRs of 0-4%[80,117,296,310] . However, clinical outcomes have been improved by combination of neratinib with other targeted agents, such as temsirolimus or trastuzumab[117,296,310] . Trials of neratinib have shown high ORRs (up to 44%) in ERBB2-mutated cervical cancer[80,311] but very low ORRs in colorectal and bladder cancer[80].

Trastuzumab

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[41-42,46,63,312-316] .

SUPPORTING DATA

A case study reported 1 PR for a patient with ampullary carcinoma treated with trastuzumab and chemotherapy[287]. In a clinical trial in pancreatic cancer, the response rate to trastuzumab and gemcitabine was found to be similar to gemcitabine alone[317]. Similarly, a Phase 2 clinical trial of trastuzumab and capecitabine noted similar progression-free and overall survival to standard chemotherapy[101]. A series of case studies reported preferential clinical activity for trastuzumab treatment of gallbladder adenocarcinoma versus cholangiocarcinoma, with the adenocarcinoma subgroup of 9 patients achieving 1 complete response, 4 partial responses, and 3 instances of stable disease in response to regimens involving trastuzumab; all samples from responsive patients had ERBB2 amplification or overexpression, and clinical responses lasted 8-168 weeks[318]. In a Phase 2a umbrella basket trial, out of 8 patients with biliary cancer and HER2 alteration, 3 patients had a partial response and 5 patients had stable disease[319]. Case reports have described responses for patients with HER2-positive cholangiocarcinoma to treatment with trastuzumab and paclitaxel[320] or trastuzumab alone[321].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
D769Y

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[48,314,322-326] .

SUPPORTING DATA

A Phase 2A MyPathway study evaluating combination of trastuzumab and pertuzumab for patients with ERBB2-positive (amplification or overexpression) biliary cancer reported an ORR of 22.5% (9/40)[327]. In a retrospective study of 8 patients with HER2-positive gallbladder cancer treated with HER2-directed therapies, one patient receiving pertuzumab and trastuzumab combination therapy experienced stable disease lasting >8 weeks[318]. A patient with ERBB2-amplified cholangiocarcinoma treated with trastuzumab combined with pertuzumab achieved a rapid and durable (>12 months) response[328].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

10 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

TARGETS PD-L1, PD-1, CTLA-4

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy), Meldola (Italy)

NCT04261439

PHASE 1

A Phase I/Ib Study of NIZ985 Alone and in Combination With Spartalizumab

TARGETS PD-1

LOCATIONS: Taipei (Taiwan), Chuo ku (Japan), Essen (Germany), Napoli (Italy), Barcelona (Spain), Madrid (Spain), California, Texas

NCT04215978

PHASE 1

Safety and Preliminary Effectiveness of BGB-A445 in Combination With Tislelizumab in Participants With Advanced Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: Changhua (Taiwan), Taipei (Taiwan), Tianan (Taiwan), Hangzhou (China), Shanghai (China), Changsha (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Gyeongju (Korea, Republic of)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

NCT05102006

PHASE 1/2

Phase Ib/II Clinical Study of LBL-007 in Treatment of Advanced Malignant Tumors

TARGETS
LAG3, PD-1

LOCATIONS: Nanchang (China), Changzhou (China), Guangzhou (China), Changsha (China), Wuhan (China), Bengbu (China), Linyi (China), Zhengzhou (China), Jinan (China), Chongqing (China)

NCT03744468

PHASE 1/2

Study of BGB-A425 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIM-3

LOCATIONS: Busan (Korea, Republic of), Ulsan (Korea, Republic of), Cheongju (Korea, Republic of), Suwon (Korea, Republic of), Incheon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang (Korea, Republic of), Perth (Australia), Hervey Bay (Australia)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

GENE
ATM

ALTERATION
splice site 3077+1G>A, T656fs*2, Q2714*

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05514132

PHASE 1

A Study to Evaluate the Safety and Pharmacokinetics of Ceralasertib in Combination With Durvalumab in Chinese Patients With Advanced Solid Tumours

TARGETS
PD-L1, ATR

LOCATIONS: Beijing (China), Shandong (China)

NCT05469919

PHASE 1

An Open-Label Phase 1 Study of Ceralasertib in Japanese Patients With Advanced Solid Malignancies

TARGETS
ATR

LOCATIONS: Chuo-ku (Japan)

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Kashiwa (Japan), Singapore (Singapore), Bellinzona (Switzerland), Edmonton (Canada)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, EGFR, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

GENE
CHEK2

ALTERATION
T387A

RATIONALE
On the basis of clinical evidence in prostate and other solid cancers, CHEK2 loss or inactivation may confer sensitivity to PARP inhibitors.

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

NCT04972110

PHASE 1/2

Study of RP-3500 With Niraparib or Olaparib in Advanced Solid Tumors

TARGETS
PARP, ATR

LOCATIONS: Utah, Minnesota, Michigan, Connecticut, New York, Maryland, Texas

GENE
ERBB2

ALTERATION
D769Y

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Osakasayama (Japan), Nagoya-shi (Japan), Kawasaki-shi (Japan), Chuo-Ku (Japan), Tokyo (Japan), Kashiwa-shi (Japan), Poznan (Poland), Berlin (Germany)

NCT04886804

PHASE 1

A Study to Test Different Doses of BI 1810631 in People With Different Types of Advanced Cancer (Solid Tumours With Changes in the HER2 Gene)

TARGETS
ERBB2

LOCATIONS: Guangzhou (China), Tokyo, Chuo-ku (Japan), Chiba, Kashiwa (Japan), Amsterdam (Netherlands), California, Texas

NCT04946968

PHASE 2

Phase-2 Dacomitinib Study on Patients With EGFR-Driven Advanced Solid Tumours With Low EGFR-AS1 lncRNA Expr or Other Novel Emerging Biomarkers

TARGETS
ERBB4, EGFR, ERBB2

LOCATIONS: Singapore (Singapore)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, EGFR, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT05372614

PHASE 1

Testing the Safety and Tolerability of the Anti-cancer Drugs Trastuzumab Deruxtecan and Neratinib for Cancers With Changes in the HER2 Gene

TARGETS
ERBB2, EGFR, ERBB4

LOCATIONS: Wisconsin, Illinois, Missouri, Pennsylvania, Massachusetts, Texas

GENE
RNF43

ALTERATION
Q670*

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT02521844

PHASE 1

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

TARGETS
PORCN

LOCATIONS: Singapore (Singapore), Colorado, Texas, North Carolina

NCT04907851

PHASE 2

A Study to Assess RXC004 Efficacy in Advanced Solid Tumours After Progression on Standard of Care (SoC) Therapy (PORCUPINE2)

TARGETS
RANKL, PORCN, PD-1

LOCATIONS: Wollongong (Australia), Melbourne (Australia), Glasgow (United Kingdom), Sheffield (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Oxford (United Kingdom), Belfast (United Kingdom)

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

AKT3
R241W

ATM
R2832G and V2774G

CRKL
P67S

IGF1R
E1283K

JAK2
V392M

LYN
K85R

MEN1
K367N

MITF
K44M

MLL2
D1100E and P2349L

PIK3C2B
P771S

PTCH1
R1303C

RARA
S451R

SDHA
R31G

SETD2
H739R

TNFRSF14
S91R

Electronically signed by Matthew Hiemenz, M.D. | 20 March 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1585611-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*	***CD274*** **(PD-L1)**	*CDC73*
CDH1	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2 **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15, **24-27**	*EMSY* (C11orf30)	*EP300*	*EPHA3*
EPHB1	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1*** **Exons 4-8**
*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*	*FLCN*	*FLT1*
FLT3 **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (H3F3A)	*HDAC1*	*HGF*	*HNF1A*
HRAS **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*	*INPP4B*
IRF2	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*	*KDM5C*
KDM6A	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	***KRAS***

Electronically signed by Matthew Hiemenz, M.D. | 20 March 2023
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FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*	*MTAP*
MTOR **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*	***NF1***
NF2	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**	***PDGFRB*** **Exons 12-21, 23**
PDK1	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PRKN* (PARK2)	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. *Note:* A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

KMT2D (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.6.0

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