FOUNDATIONONE®LIQUID CDx

PATIENT
Li, Tsung-Ching

TUMOR TYPE
Unknown primary adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
13 June 2023

ORDERED TEST #
ORD-1646739-01

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 Unknown primary adenocarcinoma
NAME Li, Tsung-Ching
DATE OF BIRTH 29 August 1956
SEX Male
MEDICAL RECORD # 46801701

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 TCL 8/29/1956
SPECIMEN TYPE Blood
DATE OF COLLECTION 02 June 2023
SPECIMEN RECEIVED 07 June 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.

MET amplification
MYC amplification - equivocal†
CTCF rearrangement exon 4
TP53 L145Q
VEGFA amplification - equivocal†

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cabozantinib** (p. 10), **Capmatinib** (p. 10), **Crizotinib** (p. 11), **Tepotinib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (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	None	None
10 Trials see p. 12		
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).**	

GENOMIC FINDINGS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET - amplification	-	None	Cabozantinib
			Capmatinib
			Crizotinib
			Tepotinib
8 Trials see p. 14			

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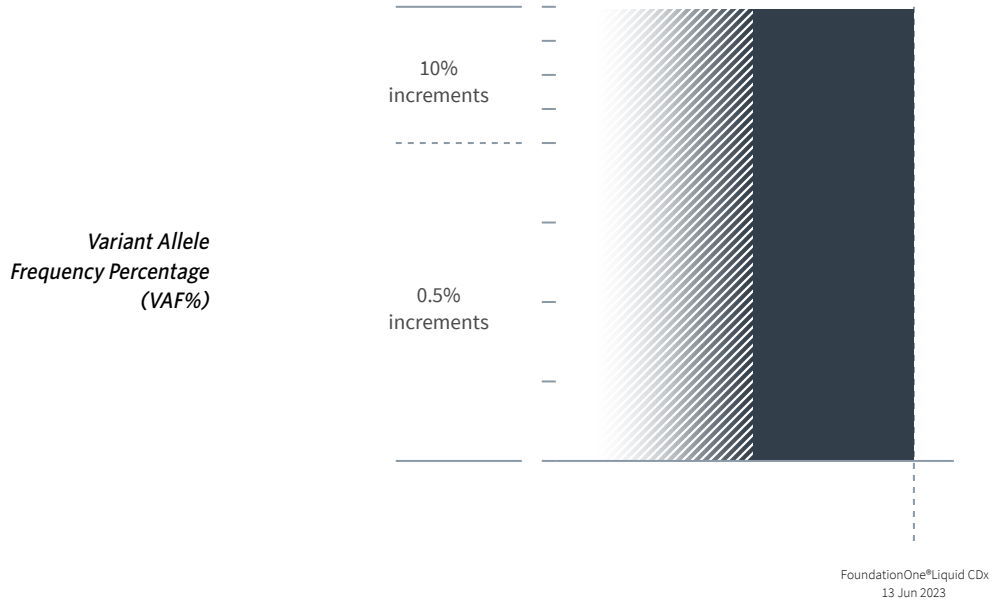
GENOMIC FINDINGS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MYC - amplification - equivocal	-	None	None
8 Trials see p. 16			

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-1646739-01 VAF%
Blood Tumor Mutational Burden		10 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		48%
MET	amplification	Detected
MYC	amplification	Detected
CTCF	rearrangement exon 4	10.8%
TP53	● L145Q	41.1%
VEGFA	amplification	Detected

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.

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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). Published data investigating the prognostic implications of TMB have mainly been investigated in the context of tissue TMB. In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[12], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[13]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[12,14], several other large studies did find a strong link[15-18]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[19-20] and with microsatellite instability (MSI)[20], which in turn has been reported to correlate with better prognosis[21-28]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[29-32] and bladder cancer[33], it is also linked with improved prognosis in patients with these tumor types[30].

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[34-35] and cigarette smoke in lung cancer[36-37], treatment with temozolomide-based chemotherapy in glioma[38-39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19,30,40-42], and microsatellite instability (MSI)[19,30,42]. 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 higher sensitivity for identifying genomic alterations. Such specimens are at a lower 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[43-48].

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)[49]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[50], Ewing sarcoma and osteosarcoma[51], prostate cancer[46], breast cancer[52], leiomyosarcoma[53], esophageal cancer[54], colorectal cancer[55], and gastrointestinal cancer[56].

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[57], 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[58-59].

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GENE
MET

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[60-63], gastroesophageal cancer[64], glioblastoma[65], and carcinoma of unknown primary[66]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified cholangiocarcinoma[67], as well as MET-amplified NSCLC, both as a monotherapy[68] and in combination with an EGFR TKI for patients with concurrent activating EGFR mutations[69-71]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[72] and NSCLC[73] as a monotherapy as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[74]. Savolitinib elicited responses for patients with MET-amplified gastric cancer either alone or in combination with docetaxel[75-76]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[77]. Patients with MET-amplified NSCLC[78] or MET-amplified gastric cancer[79] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[80]. The Phase 2 LUMINOSITY study of the MET antibody drug conjugate telisotuzumab vedotin (teliso-V) reported a 37% (19/52) ORR for patients with non-squamous EGFR-wildtype tumors; lower ORRs were observed for patients with squamous (11%, 3/27) or non-squamous EGFR-mutated (12%, 5/43) tumors[81]. A Phase 1 study showed that teliso-V plus osimertinib yielded an ORR of 56% (10/18) for patients with EGFR-mutated MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with an EGFR L858R mutation and 67% (6/9) for those with an EGFR exon 19 deletion[82].

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of MET has been found in several tumor types, with the highest incidences in esophageal carcinoma (3.3%), ovarian serous cystadenocarcinoma (3.2%), stomach adenocarcinoma (3.0%), and lung adenocarcinoma (2.2%) datasets; lower incidences were observed in various other tumor types (cBioPortal, Oct 2022)[83-84]. Overexpression of MET mRNA and protein has been observed in a number of cancers[85-87]. MET amplification has been associated with poor prognosis in gastroesophageal adenocarcinoma, gastric and esophageal cancer[64,88-93]. Increased MET expression has been associated with poor prognosis in cutaneous malignant melanoma[94], gallbladder adenocarcinoma[95], lung large cell neuroendocrine carcinoma[96], and breast cancer[97-99]. The prognostic value of MET amplification or expression in non-small cell lung cancer (NSCLC)[100-107], endometrial carcinoma[108-111] or colon cancer[112-114] have yielded conflicting results, although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival in NSCLC[115].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[116-117]. MET has been reported to be amplified in cancer[84], with amplification positively correlating with protein expression in some cancer types[85-87,101,118] and associating with therapeutic response to MET inhibitors in a variety of cancer types[60-62,64-66,119-120].

GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicates that MYC activation may predict sensitivity to the pan-MYC inhibitor OMO-103; a Phase 1 study for patients with solid tumors reported 7 SDs (n=18), including 8% tumor reduction in a patient with pancreas adenocarcinoma[121]. Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[122-123], CDK2[124], Aurora kinase A[125-132], Aurora kinase B[133-136], glutaminase[137-140], or BET bromodomain-containing proteins[141-144], as well as agents targeting both HDAC and PI3K[145-147]. Exploratory biomarker analysis in a Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer, but not for patients without MYC overexpression[148]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[149].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[150-151]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[152-153].

FREQUENCY & PROGNOSIS

MYC amplification has been reported in various solid tumors including breast (9.6%), ovarian (6.7%), melanoma (5.8%), endometrial (5.5%), non-small cell lung (5.5%), prostate (4.7%), esophagogastric (4.4%), and colorectal (3.9%) cancer[154]. In patients with some tumor types, such as lung cancer, MYC amplification has been associated with improved relapse-free survival, whereas in patients with other cancer types, such as prostate cancer, MYC overexpression has been associated with cancer recurrence[123-124,135,155-156].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[157]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[158]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[157,159-160].

GENE
CTCF

ALTERATION
rearrangement exon 4

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CTCF.

FREQUENCY & PROGNOSIS

Somatic mutations in CTCF are infrequently reported in most cancers, but have been observed more commonly (24%) in uterine corpus endometrial carcinoma (cBioPortal, 2023)[83-84]; nearly half of the observed mutations were truncating, suggesting a tumor suppressor role for CTCF in this disease. In addition, CTCF has been found to act as a tumor suppressor in breast cancer cell line studies[161-162].

FINDING SUMMARY

CTCF encodes an 11-zinc-finger protein that is implicated in various regulatory roles, including gene activation and repression, imprinting, insulation, methylation, and X chromosome inactivation[163]. CTCF plays a role in transcriptional regulation of a number of key cancer-associated genes, including the oncogene MYC[164] and tumor suppressor TP53[165], via maintenance of local DNA methylation status. Decreased expression levels of CTCF and/or BORIS, another 11-zinc-finger transcriptional regulator, were reported to be closely associated with global DNA methylation variability and decreased OS in epithelial ovarian cancer[166-167].

GENE
TP53

ALTERATION
L145Q

HGVS VARIANT
NM_000546.4:c.434T>A (p.L145Q)

VARIANT CHROMOSOMAL POSITION
chr17:7578496

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[168-171] or p53 gene therapy such as SGT53[172-176]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[177]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[178]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[179]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[180]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[75]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[181]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[182]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[176]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[183]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[184].

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[185]. TP53 loss of heterozygosity (LOH) is frequently seen in tumors and often occurs when one copy of TP53 harbors a mutation; in some tumors, LOH is correlated with progression[186-189]. While the prognostic significance of TP53 alteration or dysregulation varies according to tumor type, studies have shown an association with poor prognosis for patients with breast cancer[190-192], endometrial cancer[193-194], HNSCC[195-197], or urothelial cancer[198-199]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[200]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[201].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[202]. Alterations such as seen here may disrupt TP53 function or expression[203-207].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 hereditary cancer-predisposing syndrome (ClinVar, Apr 2023)[208]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[209-211], including sarcomas[212-213]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[214] to 1:20,000[213]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[215]. In the appropriate clinical context, germline testing of TP53 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[216-221]. 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[216-217]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[222]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[220,223-224]. 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
VEGFA

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The approved VEGFA-targeted agents bevacizumab and ziv-aflibercept have demonstrated efficacy in multiple tumor types; however, expression or amplification of VEGFA has not been established as a reliable biomarker of response to these therapies[225-256]. Preclinical hepatocellular carcinoma (HCC) models with VEGFA amplification showed increased sensitivity to sorafenib, and a small retrospective study reported significantly increased OS for 7 patients with VEGFA-amplified HCC treated with sorafenib[257]. However, a prospective biomarker study showed that VEGFA amplification detected by circulating cell-free DNA was not significantly associated with DCR, time to progression, or median OS for patients with HCC treated with first-line sorafenib[258]. It is currently not known if VEGFA amplification predicts response to other inhibitors targeting VEGFRs.

FREQUENCY & PROGNOSIS

In the TCGA datasets, VEGFA amplification was observed in 13% of esophageal carcinoma, 7% of stomach adenocarcinoma, 3% of lung adenocarcinoma, 2% of pancreatic adenocarcinoma, and 1% of colorectal adenocarcinoma (CRC) cases[19,259-260]. Amplification of the 6p12 locus, where VEGFA is located, has been observed in 3% of CRC cases[261]. Increased plasma VEGF-A levels have been associated with decreased overall survival in patients with non-small cell lung cancer (NSCLC)[229,240] and with worse prognosis in patients with cervical cancer[262], and VEGF expression was reported to be correlated with higher stage in hypopharyngeal SCC[263]. There have been conflicting reports regarding the value of serum VEGF-A levels as a prognostic indicator in patients with gastric cancer[225,264], gastroesophageal junction cancer[264], non-small cell lung cancer (NSCLC)[229,240], pancreatic ductal adenocarcinoma[265-267]; furthermore, it has not been shown that VEGFA amplification or expression in tumor cells results in increased plasma levels of VEGF-A[240].

FINDING SUMMARY

VEGFA (vascular endothelial growth factor A) encodes a ligand that promotes angiogenesis through the receptor tyrosine kinases VEGFR1 and VEGFR2[268]. VEGFA promotes tumor growth by activating both autocrine VEGFR signaling in tumor cells and paracrine signaling to fibroblasts and immune cells in the tumor microenvironment[268]. VEGFA has been reported to be amplified in cancer[84], and is associated with response to sorafenib[257].

Cabozantinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[269-270] , as well as by extensive preclinical data[271-277] .

SUPPORTING DATA

A randomized Phase 2 discontinuation study of cabozantinib in 9 solid tumor types reported ORRs of 0% to 22% and response durations of 3.3 to 11.2 months across cohorts with ORRs of 10% or greater observed for patients with ovarian cancer (22% [15/69, 1 CR]), metastatic breast cancer (14% [6/44]), and non-small cell lung cancer (NSCLC) (10% [6/60])[278-279] . A Phase 1 study of cabozantinib for advanced solid tumors reported a 17% (4/23) ORR in the dose escalation cohort and an ORR of 20% (4/20) and a DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[280]. In the context of studies for specific solid tumors, the randomized Phase 3 EXAM study for patients with advanced medullary thyroid cancer reported an association of cabozantinib with improved PFS compared with placebo (11.2 vs. 4.0 months, HR=0.28) and a higher ORR (28% vs. 0%), with PFS improvement observed regardless of RET mutation status[281]. The randomized Phase 3 CELESTIAL study for patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib reported significantly longer OS (10.2 vs. 8.0 months, HR=0.76) and PFS (5.2 vs. 1.9 months, HR=0.44) as well as an increased ORR (3.8% vs. 0.4%) with cabozantinib when compared to placebo[282]. The Phase 2 CABOSUN trial of first line cabozantinib versus sunitinib for patients with intermediate- or poor-risk advanced clear cell renal cell carcinoma demonstrated significantly improved median PFS (8.2 vs. 5.6 months, HR=0.66), prolonged median OS (30.3 vs. 21.8 months), and higher ORR (33% [26/79] vs. 12% [9/78]) with cabozantinib compared with sunitinib[283]. The Phase 2 CABONE study of cabozantinib reported ORRs of 26% (10/39) for patients with advanced Ewing sarcoma and 12% (5/42) for patients with advanced osteosarcoma[284].

Capmatinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[73,285-289] , hepatocellular carcinoma[72], renal cell carcinoma[290], and gastric cancer[75], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[291-293] or MET exon 14 skipping alterations[68,292] as well as in combination with EGFR inhibitors for patients with MET amplification[69-71] . Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with MET-amplified glioblastoma (n=10)[294], MET-overexpressing gastric cancer (n=9)[295], or other advanced solid tumors with MET amplification or overexpression (n=11)[295-296] .

Crizotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumor (IMT), and pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[60-62,297-298] , gastric cancer[119], gastroesophageal cancer[64], glioblastoma[65], and carcinoma of unknown primary[66], as well as in patients with MET-mutated cancers, including NSCLC[269,299-303] , renal cell carcinoma (RCC)[304], and histiocytic sarcoma[299]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[269,299,301-303,305] .

SUPPORTING DATA

Crizotinib has demonstrated efficacy for patients with NSCLC and ALK rearrangements[306-310] , ROS1 rearrangements[311-315] , an NTRK1 fusion[316], or MET activation[60-62,269,297-298,300-303,317-323] . Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[324] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[64-66] . While a Phase 1b study evaluating crizotinib to treat patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) for patients with lymphoma and inflammatory myofibroblastic tumors (IMT), respectively, an ORR of 11.8% (2/17) was reported for patients with other types of tumors[325]. Whereas median PFS and median OS were not reached for patients with lymphoma or IMT, median PFS was 1.3 months and median OS was 8.3 months for patients with other tumor types, and the median duration of treatment was ~1 month relative to 1-3 years for patients with lymphoma or IMT[325]. A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 14/79 patients, including nine CRs and five PRs; response was enriched for patients with activating alterations in ALK[326].

Tepotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[73,285-289] , hepatocellular carcinoma[72], renal cell carcinoma[290], and gastric cancer[75], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[73] and MET exon 14-skipping alterations[327-328] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[288-289] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[72,329-331] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[332]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[333].

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)

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)

NCT04892498

PHASE 2

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

TARGETS
PD-1

LOCATIONS: Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

GENE
MET

ALTERATION
amplification

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

NCT04647838

PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

LOCATIONS: Cheonan (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT05439993

PHASE 1/2

Tepotinib Plus Paclitaxel in MET Amplified or MET Exon 14 Alterated Gastric and GEJ Carcinoma

TARGETS
MET

LOCATIONS: Gyeonggi-do (Korea, Republic of)

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)

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)

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Villejuif (France), Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

NCT04693468

PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

NCT05038839

PHASE 1

Cabozantinib and Pamiparib for the Treatment of Advanced of Refractory Solid Tumors

TARGETS
MET, ROS1, RET, VEGFRs, PARP

LOCATIONS: Texas

GENE
MYC

ALTERATION
amplification - equivocal

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT05253053

PHASE 1/2

Study to Evaluate the Efficacy and Safety of TT-00420 as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B, PD-L1

LOCATIONS: Jinan (China), Beijing (China)

NCT04983810

PHASE 1/2

A Study to Investigate Fadraciclib (CYC065), in Subjects With Advanced Solid Tumors and Lymphoma

TARGETS
CDK2, CDK9

LOCATIONS: Seoul (Korea, Republic of), Barcelona (Spain), California, Texas

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Montana, California, Colorado, Arizona, Michigan, Texas

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Colorado, Illinois, Texas, North Carolina, Georgia

NCT04742959

PHASE 1/2

Crossover Relative Bioavailability and Dose Escalation Study of TT-00420 Tablet in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: California, Illinois, Ohio, Texas, New Jersey

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT04840589

PHASE 1

Testing the Combination of ZEN003694 and Nivolumab With or Without Ipilimumab in Solid Tumors

TARGETS
PD-1, CTLA-4, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Ohio, Pennsylvania, New York, Maryland

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

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.

ALK
NM_004304.4: c.2035C>T (p.P679S)
chr2:29497971

DAXX
NM_001350.4: c.1370_1372del (p.E457del)
chr6:33287880-33287883

EPHB1
NM_004441.4: c.1785T>G (p.I595M)
chr3:134898727

ERBB4
NM_005235.2: c.1426A>G (p.T476A)
chr2:212566755

ERRFI1
NM_018948.3: c.170A>C (p.N57T)
chr1:8075400

FANCG
NM_004629.1: c.657G>C (p.E219D)
chr9:35077088

FGFR4
NM_213647.3: c.826G>A (p.D276N)
chr5:176519420

GATA3
NM_001002295.1: c.539A>G (p.E180G)
chr10:8100565

KMT2D (MLL2)
NM_003482.4: c.12223C>T (p.L4075F)
chr12:49426265

LTK
NM_002344.5: c.826G>A (p.G276S)
chr15:41803533

LYN
amplification

MET
NM_000245.2: c.3134C>T (p.P1045L)
chr7:116415040

MST1R
NM_002447.2: c.2205A>C (p.L735F)
chr3:49934302

MUTYH
NM_001048171.1: c.673G>A (p.V225I)
chr1:45798136

NBN
amplification

NOTCH1
NM_017617.3: c.7655A>T (p.E2552V)
chr9:139390536

NTRK3
NM_002530.2: c.1805A>T (p.K602M)
chr15:88476327

RAD21
amplification

RET
NM_020975.4: c.313T>A (p.S105T)
chr10:43596146

TET2
NM_001127208.2: c.4538A>G (p.E1513G)
chr4:106196205

TSC2
NM_000548.3: c.5378G>A (p.R1793Q)
chr16:2138565

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***

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) 7.9.0

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