FOUNDATIONONE®LIQUID CDx

PATIENT	TUMOR TYPE	REPORT DATE
Hsu, Cho-Chiao	Unknown primary undifferentiated small cell carcinoma	31 Jan 2022
	COUNTRY CODE TW	ORDERED TEST # ORD-1285685-01

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 undifferentiated small cell carcinoma
NAME Hsu, Cho-Chiao
DATE OF BIRTH 15 December 1941
SEX Female
MEDICAL RECORD # 12406450

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 CCH 12/15/1941
SPECIMEN TYPE Blood
DATE OF COLLECTION 19 January 2022
SPECIMEN RECEIVED 21 January 2022

Biomarker Findings

Blood Tumor Mutational Burden - 21 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.

FBXW7 K374*
MET amplification - equivocal†
AKT2 amplification
CCNE1 amplification - equivocal†
RAF1 amplification, RAF1-PHACTR1 non-canonical fusion
CDKN2A/B p16INK4a S12*
ERBB3 amplification - equivocal†
MLL2 P562fs*6, S3614*
TP53 E198*

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TP53*** **E198*** (p. 12)
- Targeted therapies with potential clinical benefit **approved in another tumor type: Cabozantinib** (p. 13), **Capmatinib** (p. 13), **Crizotinib** (p. 14), **Everolimus** (p. 15), **Temsirolimus** (p. 15), **Tepotinib** (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: ***MLL2*** **P562fs*6, S3614*** (p. 11)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 21 Muts/Mb	None	None
10 Trials see p. 17		
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)
FBXW7 - K374*	16.6%	None	Everolimus
			Temsirolimus
9 Trials see p. 22			

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PATIENT
Hsu, Cho-Chiao

TUMOR TYPE
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TW

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ORD-1285685-01

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET -	amplification - equivocal	-	None	Cabozantinib
				Capmatinib
				Crizotinib
				Tepotinib
10 Trials see p. 24				
AKT2 -	amplification	-	None	None
10 Trials see p. 19				
CCNE1 -	amplification - equivocal	-	None	None
1 Trial see p. 21				
RAF1 -	amplification	-	None	None
	RAF1-PHACTR1 non-canonical fusion	0.15%		
8 Trials see p. 26				

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.

MLL2 - P562fs*6, S3614* p. 11

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.

CDKN2A/B - p16INK4a S12* p. 10
ERBB3 - amplification - equivocal p. 11
MLL2 - P562fs*6, S3614* p. 11
TP53 - E198* p. 12

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.

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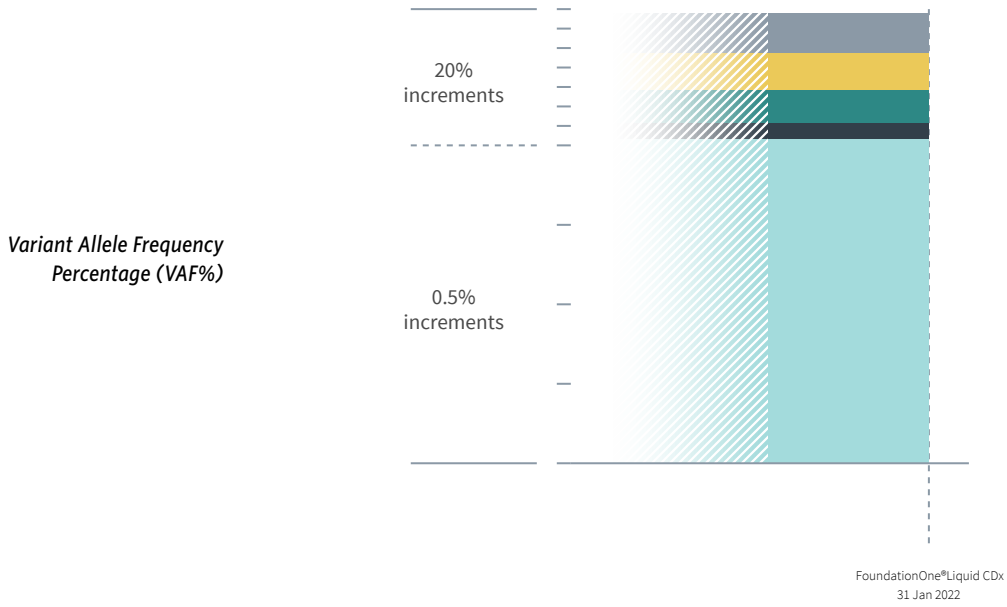

HISTORIC PATIENT FINDINGS		ORD-1285685-01 VAF%
Blood Tumor Mutational Burden		21 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		44%
FBXW7	● K374*	16.6%
MET	amplification	Detected
AKT2	amplification	Detected
CCNE1	amplification	Detected
RAF1	amplification	Detected
	RAF1-PHACTR1 non-canonical fusion	0.15%
CDKN2A/B	● p16INK4a S12*	33.6%
ERBB3	amplification	Detected
MLL2	● S3614*	37.8%
	● P562fs*6	8.7%

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HISTORIC PATIENT FINDINGS		ORD-1285685-01 VAF%
TP53	E198*	41.0%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, 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. 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.

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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
21 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In 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 to 16 Muts/Mb[1]. In 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[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. In 1 retrospective study of patients with advanced neuroendocrine tumors not treated with immunotherapy, tumor mutational burden (TMB)-high (≥10 Muts/Mb) was not correlated with any significant difference in OS compared with TMB-low (≤ 10 Muts/Mb) measured in tissue samples (10.4 vs. 6.4 months, adjusted HR = 0.83)[8]. The impact of TMB on the prognosis and clinicopathological features of lung neuroendocrine cancers is unclear; large cell neuroendocrine carcinoma (LCNEC) cases with small cell lung cancer-like molecular features were reported to have significantly higher proliferative activity, as well as a trend toward better clinical benefit from treatment with chemotherapy, than non-small cell lung cancer-like tumors, but the average TMB was not significantly different between the two subsets of LCNEC[9]. MCPyV-negative Merkel cell carcinoma (MCC), associated with higher TMB, has been reported to have a higher number of predicted tumor neoantigens and a significantly higher UV mutation signature than MCPyV-positive MCC[10-11]. Within MCPyV-negative MCC tumors, the mutational burden has been reported to be significantly higher in PD-L1-positive tumors (more than 1% positive tumor and macrophage cells by immunohistochemistry) than in PD-L1-negative tumors[12].

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[1-3].

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].

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GENE
FBXW7

ALTERATION
K374*

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
1120A>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[41-42]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[45].

— Nontargeted Approaches —

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[46].

FREQUENCY & PROGNOSIS

Across publicly available datasets, FBXW7 mutation has been reported in 0% of pancreatic neuroendocrine tumors (NETs), 2.3% (1/44) of prostate neuroendocrine carcinomas, and 3.2% of small cell lung cancer samples (cBioPortal, Oct 2021)[5-6]. A sequencing study of gastrointestinal NETs reported FBXW7 mutations exclusively in rectal NETs (5/69, 7.2%)[47]. Another study of small intestinal NETs reported both FBXW7 mutation (1/52, 1.9%) and FBXW7 loss of heterozygosity (1/52, 1.9%)[48]. The frequency of rearrangement in neuroendocrine carcinoma has not been evaluated (cBioPortal, COSMIC, PubMed, Oct 2021)[5-7]. Published data investigating the prognostic implications of FBXW7 alteration in neuroendocrine carcinoma are limited (PubMed, Oct 2021). Reduced FBXW7 expression has been associated with poor prognosis in some cancers such as colorectal cancer, gastric cancer, esophageal SCC, cervical SCC, melanoma, and non-small cell lung carcinoma[49-56].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[57]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[57-58]. Alterations such as seen here may disrupt FBXW7 function or expression[58-65].

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GENE
MET

ALTERATION
amplification - equivocal

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[66-69], gastroesophageal cancer[70], glioblastoma[71], and carcinoma of unknown primary[72]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[73-74] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[75-77]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[78] and NSCLC[79] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[80-82] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[83] and gastric cancer either alone or in combination with docetaxel[84-85]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[86]. Patients with MET-amplified NSCLC[87] or MET-amplified gastric cancer[88] 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[89]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[90]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[91].

FREQUENCY & PROGNOSIS

MET alterations have not been reported in any of 15 ovarian or 21 prostate small cell carcinomas analyzed in the COSMIC dataset (Mar 2021)[7]. MET alterations have not been reported in any of the 8 cervical small cell carcinomas analyzed in the COSMIC dataset (Mar 2021)[7]. MET expression has been reported frequently (in >25% of cases) in pulmonary neuroendocrine cancers, including large cell neuroendocrine carcinomas, SCLCs, and both typical and atypical carcinoids[92-94]. The frequency of MET amplification in neuroendocrine carcinoma has not been evaluated (cBioPortal, PubMed, Jun 2021)[5-6]. A study of 83 SCLC cases reported a trend toward correlation between MET expression and shorter OS, which reached significance in patients with limited disease-stage tumors[94]. Published data investigating the prognostic implications of MET alterations in neuroendocrine carcinoma are limited (PubMed, Jun 2021).

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[95-96]. MET has been reported to be amplified in cancer[6], with amplification positively correlating with protein expression in some cancer types[97-101] and associating with therapeutic response to MET inhibitors in a variety of cancer types[66-68,70-72,102-103].

GENE
AKT2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or activation of AKT2 may promote AKT-mTOR pathway activation and may predict sensitivity to inhibitors of the AKT and downstream mTOR pathways. Clinical benefit has been achieved in 1 patient with AKT2 amplification treated with an mTOR inhibitor[104]. In preclinical studies, the AKT inhibitor MK-2206 showed evidence of enhancing anti-tumor activity of other chemotherapeutic agents in lung and ovarian tumor cells[105].

FREQUENCY & PROGNOSIS

The incidence of AKT2 amplification has not been extensively assessed in neuroendocrine carcinoma subtypes (cBioPortal, Dec 2021)[5-6]. One study reported amplification of AKT2 in 5/48 (10.4%) of small intestine neuroendocrine tumors[106]. Published data investigating the prognostic implications of AKT2 alterations in neuroendocrine tumors are limited (PubMed, Dec 2021).

FINDING SUMMARY

AKT2 encodes an intracellular serine/threonine kinase that is also known as PKB-beta. AKT2 is one of three members of the AKT gene family, and activation of AKT2 has been implicated in multiple malignancies[107-108]. AKT isoforms appear to have different roles in tumorigenesis; AKT1 appears to contribute to the initiation of tumors, whereas AKT2 promotes invasion and metastasis in breast tumors[109]. Although AKT2 amplification has been reported to associate with AKT2 overexpression[110-112], studies in various cancers suggest that AKT2 phosphorylation may have greater clinical relevance than AKT2 amplification or mRNA overexpression[113-114].

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GENE
CCNE1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1-WEE1 pathway[115-116] and cyclin E1 promotes cell cycle progression in a complex with CDK2[117], clinical and preclinical studies have investigated inhibitors of CHK1, ATR, CDK2, and WEE1 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade serous ovarian carcinoma (HGSOC) with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[118]. Studies of the WEE1 inhibitor adavosertib observed PRs in patients with CCNE1-amplified HGSOC and ovarian cancer[119-120]. Similarly, in a Phase 2 study of patients with CCNE1-amplified solid tumors, adavosertib elicited an ORR of 26% with PRs reported for patients with ovarian cancer, urothelial carcinoma, or melanoma[121]. Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[122-123], CDK2[124], or WEE1[116,125]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[126-129]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[130].

FREQUENCY & PROGNOSIS

CCNE1 alterations were reported in 9% (28/320) of neuroendocrine tumors in one genomic study[131]. In one study of lung neuroendocrine tumors, including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma, cyclin E was overexpressed in 21% (4/19) large cell neuroendocrine carcinoma samples and 71% (25/35) of SCLC samples; overexpression of cyclin E was associated with advanced tumor stage and nodal metastasis[132]. In a study of gastroenteropancreatic neuroendocrine tumors, high cyclin E expression was not a significant independent prognostic marker, however, patients with low p27 combined with high cyclin E expression had significantly worse overall survival than patients with high p27 combined with low cyclin E expression[132]. Another study examining neuroendocrine carcinoma of the lung reported that cyclin E1 expression was associated with Skp2 expression, observed in 86% of high grade neuroendocrine carcinomas[133]. High cyclin E expression alone, or in combination with decreased p27 expression, has been associated with shorter survival of gastroenteropancreatic neuroendocrine tumor patients[132,134].

FINDING SUMMARY

CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[117]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[135-136]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[137-138]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[117,139].

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GENE
RAF1

ALTERATION
amplification, RAF1-PHACTR1 non-canonical fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

RAF1 amplification may predict sensitivity to pan-RAF inhibitors. The addition of sorafenib to chemotherapy improved PFS for patients with melanoma and RAF1 copy number gains (HR=0.37, p=0.025) in a retrospective analysis[140]. A retrospective study reported RAF1 expression as a predictor of improved OS (HR=1.84) and tumor-free survival (HR=1.32) for patients with hepatocellular carcinoma treated with adjuvant sorafenib in multivariate analyses[141]. RAF1 activating rearrangements may predict sensitivity to pan-RAF and MEK inhibitors. A patient with RAF1-rearranged pancreatic cancer achieved a PR to sorafenib in combination with the glutamate antagonist riluzole in a case report[142]. Case studies of patients with RAF1-rearranged tumors have reported clinical responses to MEK inhibitors, including a PR for a patient with a RAF1 fusion-positive melanoma and tumor regression for patients with RAF1-rearranged and fusion-positive melanoma[143-145], complete cytological response for a patient with anaplastic pleomorphic xanthoastrocytoma[146], and ongoing SD for a patient with pilocytic astrocytoma who had progressed on prior treatments[147].

FREQUENCY & PROGNOSIS

In small cell lung carcinomas, RAF1 amplification was not observed across 142 samples[148]; RAF1 amplifications in neuroendocrine tumors have not been evaluated in the TCGA datasets (cBioPortal, Aug 2021)[5-6]. The frequency of RAF1 fusions or rearrangements has not been extensively evaluated in neuroendocrine carcinomas (PubMed, Mar 2021). RAF1 mutations have been observed in 0-1% of small cell lung cancer (SCLC) samples[148-150], 1.9% of pancreatic carcinoid-endocrine tumors, 0% of small intestine carcinoid-endocrine tumors, and 0% (0/9) of stomach carcinoid-endocrine tumors (COSMIC, Mar 2021)[7]. Published data investigating the prognostic implications of RAF1 alterations in neuroendocrine cancers are limited (PubMed, Mar 2021).

FINDING SUMMARY

RAF1 encodes c-RAF, a member of the RAF family of signaling kinases[151]. These kinases are downstream of RAS and activate the MEK-ERK signaling pathway that promotes cell proliferation and survival[152]. RAF1 has been reported to be amplified in cancer[6] and may be biologically relevant in this context[153-154]. Variants that express the c-RAF kinase domain in the absence of the N-terminal autoinhibitory domain, whether with or without a fusion partner, have been reported to be constitutively active and shown to drive hyperactivation of the MAPK pathway, thereby exhibiting transforming activity[155-158]. One or more of the rearrangements observed here were detected as a reciprocal fusion, are not clearly in-frame, or lack a fusion partner with an oligomerization domain, and it is unclear whether such events would lead to a production of an oncogenic variant.

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GENE
CDKN2A/B

ALTERATION
p16INK4a S12*

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
35C>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[159-162]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[163-164], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[165-171]; it is not known whether CDK4/6 inhibitors would be beneficial in this case.

FREQUENCY & PROGNOSIS

Loss of CDKN2A and/or CDKN2B gene expression, either due to deletion or promoter methylation, has been reported in a variety of neuroendocrine (NE) tumors in the scientific literature, including pancreatic endocrine tumors (9%, CDKN2A), NE lung tumors (15%, CDKN2B), and various NE gastroenteropancreatic tumors (up to 44%, CDKN2A and CDKN2B)[172-174]. Loss of heterozygosity (LOH) at the chromosomal region 9p21, which contains CDKN2A and CDKN2B, has been reported to be common in small cell NE carcinomas (SCNCs), with incidences of 50% (8/16), 60% (3/5), and 40% (2/5) in SCNCs of the lung, head and neck, and gastrointestinal tract, respectively; however, a lower incidence of LOH (37%) at this region has also been reported in small cell lung cancer[175-176]. The p15.5 isoform of p15INK4b has been reported to be involved in NE lung tumor carcinogenesis independent of p16INK4a or p14ARF[173]. Loss of p14ARF has been reported in a variety of NE tumors, including 40-55% of NE lung tumors, 6% of typical carcinoids, 43% of atypical carcinoids, 50% of large cell NE carcinomas, and 73% of small cell carcinomas[173,177]. Promoter methylation of CDKN2A and CDKN2B has been reported in various NE tumors[172-173,178-180]. Studies in Merkel cell carcinoma have suggested that methylation of the p14ARF promoter may be a greater contributor to p14ARF protein loss than mutation; one study reported p14ARF methylation in 42% (8/19) of Merkel cell carcinoma cases, but no CDKN2A mutation[181-183]. CDKN2A promoter methylation (p16INK4a and p14ARF-encoding loci) in NE tumors has been associated with advanced tumor stage and poor patient outcome[178,183-184].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[185-186]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[187-188]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[189-190]. One or more alterations observed here are predicted to result in p16INK4a loss of function[191-212].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[213]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[214-215]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[216-218]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[219-221]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
ERBB3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[222-225]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Clinical and preclinical data support sensitivity of ERBB3 activating mutations to various anti-ERBB2 agents[224,226-230], but data are generally limited for ERBB3 amplification. Biomarker analyses of several Phase 3 trials have not identified an association of ERBB3 expression levels with benefit from trastuzumab-, pertuzumab-, or T-DM1-containing regimens in HER2-positive breast cancer[231-234], T-DM1 in HER2-positive gastric and gastroesophageal junction (GEJ) cancer[235], pertuzumab combined with chemotherapy in ovarian cancer[236], or afatinib in HNSCC[237]. Similarly, ERBB3 expression levels were not associated with PFS or OS from lapatinib plus capecitabine in a Phase 2 study of gastric/GEJ cancer[238] or in retrospective studies of HER2-positive breast cancer[239-241].

FREQUENCY & PROGNOSIS

In neuroendocrine cancers, ERBB3 mutation has been observed in 0-0.9% of small cell lung cancers[148-150] and was not seen in pancreatic or prostate neuroendocrine tumors[242-244]. The frequency of ERBB3 amplification in neuroendocrine cancers has not been assessed (cBioPortal, COSMIC, PubMed, Oct 2021)[5-7]. Published data investigating the prognostic implications of ERBB3 alterations in neuroendocrine cancers are limited (PubMed, May 2021).

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[245]. One study has demonstrated a weak but significant association between ERBB3 gene amplification and ERBB3 protein expression in breast cancer tissue[246].

GENE
MLL2

ALTERATION
P562fs*6, S3614*

TRANSCRIPT ID
NM_003482, NM_003482

CODING SEQUENCE EFFECT
1685_1686delCC, 10841C>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, Jan 2022)[7], and are especially prevalent in lung squamous cell carcinoma (SCC)[247] and small cell lung carcinoma (SCLC)[248]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[249]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[250]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[251].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[252]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[253]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[254].

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[255-260]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[259,261-262]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
TP53

ALTERATION
E198*

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
592G>T

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[263-266], or p53 gene therapy and immunotherapeutics such as SGT-53[267-271] and ALT-801[272]. 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[273]. 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[274]. 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[275]. 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[276]. 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[84]. 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[277]. 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[278]. 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[271]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[279-280]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[281-282]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in a number of carcinoid-endocrine cases, including 48% (15/31) of the stomach, 9.1% of large intestine, 6.8% of pancreatic, 5.8% of lung, and 4.8% of small intestine origin; TP53 mutations were also observed in 19% of Merkel cell carcinomas, 41% (9/22) of prostate small cell carcinomas, 14% (10/72) of cervical endocrine tumors, and 63% of small cell lung cancer samples (COSMIC, Jan 2022)[7,283-290]. The frequency of TP53 mutation or loss and altered p53 levels in neuroendocrine lung tumors has been correlated with the degree of malignancy, as TP53 alterations are more frequent in the most malignant tumor types, including SCLC and large cell neuroendocrine carcinoma[291-293]. Within neuroendocrine tumors, expression of p53 has been associated with aggressive and poorly differentiated gastroenteropancreatic neuroendocrine tumors and with shorter survival in patients with high-grade neuroendocrine carcinomas[134,294-296].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[297]. Alterations such as seen here may disrupt TP53 function or expression[298-302].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) (NCCN Neuroendocrine and Adrenal Tumors, v1.2021)[303-306].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[307-309], including sarcomas[310-311]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[312] to 1:20,000[311]. 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[313]. 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[255-260]. 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[255-256]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[314]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[259,261-262]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Cabozantinib

Assay findings association

MET
amplification - equivocal

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[315-316] , as well as by extensive preclinical data[317-323] .

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])[324-325] . 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[326]. 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[327]. 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[328]. 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[329]. 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[330].

Capmatinib

Assay findings association

MET
amplification - equivocal

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[73,79-82,331] , hepatocellular carcinoma[78], renal cell carcinoma[83], and gastric cancer[84], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of capmatinib for the treatment of neuroendocrine tumors are limited (PubMed, Jun 2021). Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[74,332-333] or MET exon 14 skipping alterations[333-334] as well as in combination with EGFR inhibitors for patients with MET amplification[75-77] . 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)[335], MET-overexpressing gastric cancer (n=9)[336], or other advanced solid tumors with MET amplification or overexpression (n=11)[336-337] .

Crizotinib

Assay findings association

MET
amplification - equivocal

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), and to treat pediatric and young adult patients with ALK rearrangement-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)[66-68,338-339] , gastric cancer[102], gastroesophageal cancer[70], glioblastoma[71], and carcinoma of unknown primary[72], as well as in patients with MET-mutated cancers, including NSCLC[315,340-344] , renal cell carcinoma (RCC)[345], and histiocytic sarcoma[340]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[315,340,342-344,346] .

SUPPORTING DATA

A case study reported a patient with ALK-rearranged lung large-cell neuroendocrine carcinoma experienced a PR and PFS of 5 months with crizotinib treatment[347]. In another case, a patient with chemotherapy-pretreated ALK-rearranged lung atypical carcinoid tumor had tumor reduction after 3 months of crizotinib treatment[348]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[349-353] , ROS1 rearrangements[354-358] , an NTRK1 fusion[359], or MET activation[66-68,315,338-339,341-344,360-366] . Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[367] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[70-72] . While a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) in 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[368]. 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[368]. 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 in patients with activating alterations in ALK[369].

Everolimus

Assay findings association

FBXW7
K374*

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[370], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

Phase 3 studies demonstrated that everolimus compared with placebo significantly increased median PFS for patients with pancreatic neuroendocrine tumors (NETs) (11.0 vs. 4.6 months)[371] or with well-differentiated, nonfunctional NET of the lung or gastrointestinal tract (11.0 vs. 3.9 months)[372]. The Phase 2 ITMO study of everolimus in combination with the somatostatin analogue octreotide long-acting repeatable (LAR) in patients with advanced, previously untreated NETs of the gastroenteropancreatic tract and lung reported an ORR of 18% (9/50), and median PFS and OS of 33.6 months and 61.9 months, respectively[373]. In the RADIANT-2 Phase 3 study, for patients with a NET from various primary sites and with a history of carcinoid syndrome, addition of everolimus to the somatostatin analogue octreotide LAR resulted in a nonsignificant increase in PFS compared to the addition of placebo (16.4 vs. 11.3 months) and did not significantly change OS (29.2 vs. 35.2 months)[374-375] ; however, a subgroup analysis of patients with lung NET revealed increased median PFS (13.6 vs. 5.6 months)[376]. A Phase 2 study of pancreatic NETs after failure on systematic chemotherapy reported 9.6% PR and 67.8% SD in response to everolimus and 4.4% PR and 80% SD in response to everolimus plus octreotide LAR[377]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[378], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[379].

Temsirolimus

Assay findings association

FBXW7
K374*

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[370], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

In a Phase 2 trial, treatment of patients with advanced neuroendocrine carcinoma with temsirolimus resulted in a response rate of 5.6%; responses were correlated with baseline levels of phosphorylated mTOR[380]. In a Phase 2 study of 55 patients with advanced pancreatic neuroendocrine tumors, 37% showed an objective response to temsirolimus with bevacizumab and 49% of 49 patients evaluated for PFS showed no disease progression at 12 months[381]. A Phase 1 study of 40 evaluable patients treated with a combination therapy of lenalidomide and temsirolimus reported partial response in 2.5% (1/40) and stable disease in 48% (19/40) of cases; the median OS rate in this study was 7.8 months[382]. In a Phase 2 trial, combination of temsirolimus with bevacizumab resulted in a response rate of 41% in patients with pancreatic neuroendocrine tumors[383]. In a Phase 2 study, temsirolimus did not alter PFS in any of 85 patients with small cell lung cancer (SCLC)[384].

Tepotinib

Assay findings association

MET
amplification - equivocal

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with metastatic 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[73,79-82,331] , hepatocellular carcinoma[78], renal cell carcinoma[83], and gastric cancer[84], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of tepotinib for the treatment of neuroendocrine tumors are limited (PubMed, Aug 2021). Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[79] and MET exon 14-skipping alterations[385-386] . 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[81-82] . 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[78,387-389] . 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[390]. 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[391].

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.

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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

21 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), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Missouri, Connecticut, Texas

NCT04181788

PHASE 1/2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Nanjing (China), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chongqing (China), Beijing (China), Chuo-ku (Japan), Kopeysk (Russian Federation)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagoya (Japan), Koto ku (Japan), Singapore (Singapore), Tel Aviv (Israel), Zurich (Switzerland), Rozzano (Italy), Barcelona (Spain), Hospitalet de LLobregat (Spain)

NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/ Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Kashiwa (Japan), Afula (Israel), Jerusalem (Israel), Tel Aviv (Israel), Warszawa (Poland), Oslo (Norway)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Amsterdam (Netherlands), Napoli (Italy), Roma (Italy), Villejuif Cedex (France), Barcelona (Spain)

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NCT03192345

PHASE 1

A First-in-human Study of the Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity of SAR439459 Monotherapy and Combination of SAR439459 and Cemiplimab in Patients With Advanced Solid Tumors

TARGETS
PD-1, TGF-beta

LOCATIONS: Taipei 100 (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Heidelberg West (Australia), Melbourne (Australia), Tallinn (Estonia), Hannover (Germany), Essen (Germany), Utrecht (Netherlands)

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), Leuven (Belgium), Barcelona (Spain), California, Texas

NCT03565445

PHASE 1

A Study of ASP1948, Targeting an Immune Modulatory Receptor, in Subjects With Advanced Solid Tumors

TARGETS
PD-1, NRP1

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Tokyo (Japan), Chiba (Japan), Meldola (Italy), Modena (Italy), Newcastle upon Tyne (United Kingdom), Monza (Italy), Milano (Italy), Glasgow (United Kingdom)

NCT03799003

PHASE 1

A Study of ASP1951 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, TNFRSF18

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Daegu (Korea, Republic of), Chungcheongbukdo (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Washington, California, Nevada

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Hangzhou (China), Chongqing (China), Beijing (China), Cairns (Australia), Brisbane (Australia), Kurralta Park (Australia), Waratah (Australia), Blacktown (Australia), Wollstonecraft (Australia), Melbourne (Australia)

GENE
AKT2

ALTERATION
amplification

RATIONALE
AKT2 amplification or mutation may lead to AKT-mTOR pathway activation and may predict sensitivity to inhibitors of this pathway.

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

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)

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)

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
VEGFA, VEGFB, PIGF, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

GENE
CCNE1

ALTERATION
amplification - equivocal

RATIONALE
Strong preclinical and clinical data suggest that CCNE1 amplification may predict sensitivity to WEE1 inhibitors.

NCT03968653

PHASE 1

Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors

TARGETS
WEE1

LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Leiden (Netherlands), Barcelona (Spain)

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GENE
FBXW7

ALTERATION
K374*

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

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)

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
VEGFA, VEGFB, PIGF, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

GENE
MET

RATIONALE
Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors.

ALTERATION
amplification - equivocal

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), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), 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)

NCT03375320

PHASE 3

Cabozantinib S-malate in Treating Patients With Neuroendocrine Tumors Previously Treated With Everolimus That Are Locally Advanced, Metastatic, or Cannot Be Removed by Surgery

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Alaska, Hawaii, Oregon, Idaho, Montana

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)

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

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NCT04400474

PHASE 2

Trial of Cabozantinib Plus Atezolizumab in Advanced and Progressive Neoplasms of the Endocrine System. The CABATEN Study

TARGETS
PD-L1, MET, ROS1, RET, VEGFRs

LOCATIONS: Badalona (Spain), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Zaragoza (Spain), Santander (Spain), Oviedo (Spain), Alicante (Spain), Madrid (Spain), Murcia (Spain), Málaga (Spain)

NCT04079712

PHASE 2

Testing the Combination of XL184 (Cabozantinib), Nivolumab, and Ipilimumab for Poorly Differentiated Neuroendocrine Tumors

TARGETS
PD-1, CTLA-4, MET, ROS1, RET, VEGFRs

LOCATIONS: Utah, California, Kansas, Missouri

NCT04412629

PHASE 2

Cabozantinib in High Grade Neuroendocrine Neoplasms

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Missouri

NCT04197310

PHASE 2

Cabozantinib and Nivolumab for Carcinoid Tumors

TARGETS
PD-1, MET, ROS1, RET, VEGFRs

LOCATIONS: Massachusetts

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

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GENE
RAF1

ALTERATION
amplification, RAF1-PHACTR1 non-canonical fusion

RATIONALE
Activating RAF1 rearrangements may predict sensitivity to MEK inhibitors. RAF1 amplification may predict sensitivity to pan-RAF inhibitors.

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

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)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), Texas

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

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NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

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.

ACVR1B
amplification

AKT2
S474F

APC
D1841H

AXIN1
R739C

BCOR
S1266C

BRCA1
R1835Q

BRIP1
I857L

CALR
K385N and rearrangement

DDR2
I29M, S131F and amplification

FOXL2
Q219*

GATA6
S184N

JAK3
rearrangement

KDM5C
E1505K

MLL2
E878K, Q3967E and S3696L

PPARG
amplification

PTPRO
D975N

SDHC
amplification

SMO
amplification

SRC
E22_N23insPAE

TET2
G1861E

VHL
amplification

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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.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***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**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*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**	*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	*FAM46C*	*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*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*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)

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KRAS	*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**	*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**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*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*	*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*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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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

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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. 2021. 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.

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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

MR Suite Version 5.2.0

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