FOUNDATIONONE®CDx

PATIENT
Huang, Ching-Tzu

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
18 Mar 2022
ORDERED TEST #
ORD-1316163-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Brain glioblastoma (GBM)
NAME Huang, Ching-Tzu
DATE OF BIRTH 02 November 1974
SEX Female
MEDICAL RECORD # 25549331

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

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-06813A (PF22030)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 19 February 2022
SPECIMEN RECEIVED 08 March 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

BRAF V600E
ATM Q2942fs*10
CDKN2A/B CDKN2A loss, CDKN2B loss
JAK1 V310I
MTAP loss
SETD2 Y2312*

3 Disease relevant genes with no reportable alterations: ***EGFR, IDH1, PDGFRA***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Dabrafenib + Trametinib** (p. 9), **Vemurafenib + Cobimetinib** (p. 15)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 0 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)	
BRAF - V600E	none	Dabrafenib + Trametinib	2A
		Vemurafenib + Cobimetinib	2A
		Dabrafenib	
		Encorafenib + Binimetinib	
		Selumetinib	
		Trametinib	
		Vemurafenib	
10 Trials *see p. 18*			
ATM - Q2942fs*10	none	Niraparib	
		Olaparib	
		Rucaparib	
		Talazoparib	
10 Trials *see p. 16*			

☐ *NCCN category*

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 agents 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 exhaustive. Neither the therapeutic agents 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.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[10]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
0 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[16,26-30].

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GENE
ATM

ALTERATION
Q2942fs*10

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
8824_8834delCAGGAAACTCT

VARIANT ALLELE FREQUENCY (% VAF)
40.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[47]. Clinical data in prostate cancer[48-50], gastric cancer[51], colorectal cancer[52], breast cancer[52], papillary renal cell carcinoma[53], and cholangiocarcinoma[54] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[55-62]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[63] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[64] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[65-67] and hematologic malignancies[65,68] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[69].

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 1% of glioblastoma cases[70-71]. An analysis of Grades 1-4 astrocytomas detected upregulation of ATM mRNA expression[72]. Higher expression of the ATM protein correlated with longer overall and progression-free survival in a study of 69 glioblastoma cases[73]. However, ATM gene and protein expression in glioblastoma cells has also been correlated with resistance to radiation therapy; glioma cells with lower ATM expression have been found to be more sensitive to radiation than cells with higher ATM expression[74-76]. In addition, one study reported that the ATM kinase inhibitor KU-60019 inhibited glioma cell growth and invasion and sensitized cells to radiation[76]. Preclinical studies have also shown that ATM kinase inactivation and ATM inhibitors such as LY294002 and KU-55933 increase the sensitivity of glioblastoma cells to cisplatin and temozolomide[77-79].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[80]. Loss of functional ATM promotes tumorigenesis[81]. Alterations such as seen here may disrupt ATM function or expression[82-84].

POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[85]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[86]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[80,86]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[86]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[87-92]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[91,93-94]. 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
BRAF

ALTERATION
V600E

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

VARIANT ALLELE FREQUENCY (% VAF)
43.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Patients with BRAF V600-mutated gliomas have benefited from the combination of BRAF V600-inhibitor dabrafenib and MEK-inhibitor trametinib[95-96] . In low-grade glioma cohorts, ORRs of 25-69% (9/36 and 9/13) were reported in pediatric and adult patients, respectively[95-96] . For patients with high-grade glioma, including glioblastoma, the combination of dabrafenib and trametinib elicited an ORR of 33% (15/45) and median OS of 17.6 months[96]. Patients with BRAF V600-mutated glioma have also benefited from treatment with BRAF V600-inhibitor dabrafenib or vemurafenib monotherapies with ORRs of 44% (14/32) and 25% (6/24), respectively[97-99]. In smaller studies, pediatric patients with BRAF V600E-mutated pilocytic astrocytoma have responded to the MEK-inhibitor selumetinib (29% PR, 2/7)[100], and patients with BRAF V600-mutated brain tumors have benefited from the combination of vemurafenib and mTOR inhibitor everolimus (60% DCR, 2 PR and 1 SD)[101]. In a Phase 1/2 basket trial of the second-generation BRAF-inhibitor PLX8394 in combination with cobicistat, all 3 patients with BRAF V600E-mutated glioma achieved a PR[102]. In 2 Phase 1 studies evaluating the MEK-pan-RAF dual inhibitor CH5126766, 3 patients harboring BRAF V600E mutations experienced PRs, including 2 patients with melanoma[103] and 1 patient with low-grade serous ovarian carcinoma[104].

FREQUENCY & PROGNOSIS

BRAF V600E has been reported in 0.6-6% of GBM samples[105-109], with one study reporting BRAF V600E in 54% (7/13) of epithelioid glioblastomas[110]. BRAF mutation has been detected in 60-89% of patients with pleomorphic xanthoastrocytoma (PXA) and, additionally, has been reported in patients with GBM arising from PXA[108,111-113]. Various studies have implicated BRAF alterations, including V600E and rearrangements, in the oncogenesis of pediatric low grade astrocytomas, including gangliogliomas[107,114-122]. BRAF alterations have been reported in 1-3% of gliomas including low grade gliomas[40,105-107,109,123] and glioblastomas (GBM)[70]. Studies have reported conflicting results as to whether BRAF mutations, including V600E, are more likely to be found in lower grade astrocytomas or higher grade glioblastomas[105,107,124], and the frequency of the BRAF V600E mutation in astrocytoma reported in the literature varies by cohort[125-127]. BRAF V600E is not strongly associated with prognosis in patients with astrocytoma[125,127]. While one study associated KIAA1549-BRAF fusion with improved prognosis in pediatric patients with low grade astrocytomas[128], others reported no significant association between BRAF rearrangements and outcome[129-132].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[133-134]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[135-136]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with V600D comprising the majority of the rest[135,137-138]. Mutations at V600 are Class 1 BRAF alterations that have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[135,139]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M, exhibited sensitivity to V600-targeted therapies[138,140-150]; other mutations at this position are predicted to behave similarly.

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GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

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[151-154]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[155-156], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[157-163]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[164-165], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[158,160-161,166-168].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[169] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[70] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[170-171]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[172-174]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[175]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[176]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[177]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[173,178]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[179-180].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[181-182]. 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[183-184]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[185-186]. One or more alterations observed here are predicted to result in p16INK4a loss of function[187-208]. One or more alterations seen here are predicted to result in p14ARF loss of function[191,208-211]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[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.

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GENE
JAK1

ALTERATION
V310I

TRANSCRIPT ID
NM_002227

CODING SEQUENCE EFFECT
928G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Inhibitors of the JAK-STAT pathway are under development. The JAK1/JAK2 inhibitor ruxolitinib is approved to treat myelofibrosis, and has shown efficacy in reducing symptoms in Phase 1 and 2 trials in patients with myeloproliferative disorders[222-224]. Other small molecule inhibitors of JAK1 are being investigated in preclinical studies in some types of solid tumors[225-226]. HSP90 inhibitors are also being investigated in preclinical studies to target components of the JAK-STAT pathway such as JAK1[227]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the TCGA datasets, JAK1 mutation or amplification was observed in ~1% of glioblastoma cases[70] and was not observed in any lower grade gliomas[123]. A study of 96 glioma patients reported increased levels of JAK1 protein, and JAK1 phosphorylation was higher in glioma samples than in normal brain tissue[228]. High levels of JAK1 protein were correlated with poor prognosis in glioma patients[228].

FINDING SUMMARY

The JAK1 (Janus kinase 1) gene encodes a tyrosine kinase that regulates signals triggered by cytokines and growth factors[229]. Dysregulation of JAK-STAT signaling has been implicated in a variety of epithelial tumors[230]. However, JAK-STAT signaling is required for the antiviral and antiproliferative effects of interferons[231]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[232]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[233]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[232,234-235], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[236]; dual PRMT1 and PRMT5 inhibition may be more effective[237-239]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[240-250]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[251].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[252-253]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[254], gastrointestinal stromal tumors[255], mantle cell lymphoma (MCL)[256], melanoma[257-258], gastric cancer[259], myxofibrosarcoma[260], nasopharyngeal carcinoma[261], ovarian carcinoma[252] and non-small cell lung cancer[262]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[263] or in astrocytoma[264]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[265], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[266]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[267-268], esophageal cancer[269-270], osteosarcoma[271], and CRC[272].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[273-274]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[254,275-276], thereby reducing intracellular arginine methylation[232,234,277] and altering cell signaling[276,278]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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GENE
SETD2

ALTERATION
Y2312*

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
6936T>A

VARIANT ALLELE FREQUENCY (% VAF)
14.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[279]. SETD2 has been associated with favorable prognosis in gastric cancer[280]. SETD2 has also been associated with poor prognosis in RCC and MDS[281], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[282] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[283]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[284]. SETD2 alterations such as observed here have been shown to be inactivating[285-290].

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Dabrafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor that is FDA approved as a monotherapy to treat melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[138,140-149,291] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib.

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[138,140-149,291] . A Phase 1/2 study evaluating single-agent dabrafenib for the treatment of pediatric patients with BRAF V600-mutated gliomas reported an ORR of 44% (14/32; 1 CR, 13 PR), median duration of response of 26 months, and one-year PFS rate of 85% in patients with low-grade glioma (LGG) and an ORR of 39% (9/23; 2 CR, 7 PR) and median PFS of 7.4 months in patients with histologically confirmed high-grade glioma (HGG) that was either refractory or had progressed on one or more lines of standard therapy[97,292] . In separate case studies, patients with previously treated BRAF V600-mutated LGGs and HGGs exhibited CRs for 3 months and >2 years, respectively, following treatment with single-agent dabrafenib[293-294] . A Phase 1 trial that assessed combination treatment of dabrafenib and pazopanib in 23 patients with BRAF-mutated malignancies reported an ORR of 22% (5 PRs), including 1 PR in a patient with BRAF V600E-mutated glioblastoma (GBM)[295]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[140,296-297] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[298-302] .

Dabrafenib + Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor and trametinib is a MEK inhibitor. These two therapies are FDA approved in combination to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. This combination is also approved to treat patients with non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, and to treat patients with BRAF V600E-positive anaplastic thyroid cancer (ATC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in various solid tumors and hematologic malignancies, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as dabrafenib and trametinib[301-310] .

SUPPORTING DATA

Dabrafenib combined with trametinib has shown clinical efficacy for patients with BRAF V600E-mutated high-grade gliomas (HGGs). A Phase 2 trial for recurrent or progressive glioma reported an ORR of 33% (15/45, 3 CRs, 12 PRs) with median PFS of 3.8 months and OS of 17.6 months in the HGG cohort[311]. In case studies of epithelioid glioblastoma (GBM), 3 patients experienced clinical benefit from dabrafenib plus trametinib, including 1 patient with SD ongoing for 16 months[312] and rapid clinical improvement and radiographic responses for 2 additional adult patients[313]; however, 1 patient did not respond to this regimen[314]. A patient with GBM lacking epithelioid or rhabdoid features experienced a CR from dabrafenib plus trametinib[315]. Dabrafenib plus trametinib enabled a pediatric patient with anaplastic astroblastoma to remain disease-free for 20 months[316]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[140,296-297] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[298-302] .

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

The combination of the BRAF inhibitor encorafenib and MEK inhibitor binimetinib is FDA approved to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical efficacy in the treatment of patients with BRAF V600-mutated melanoma[317-320] , and activity in colorectal, thyroid, and lung cancer[320-322] , activating alterations affecting BRAF predict sensitivity to the combination of encorafenib and binimetinib.

SUPPORTING DATA

The combination of encorafenib and binimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[317,320-322] , and has been studied primarily in the context of BRAF V600-mutated melanoma where patients treated with this combination achieved greater PFS and OS compared with encorafenib or vemurafenib monotherapy[317-318,323] . A combination of encorafenib, binimetinib, and the CDK4/6 inhibitor ribociclib in a Phase 1b trial for patients with BRAF V600-mutant cancers elicited responses in melanoma, astrocytoma, unknown carcinoma, and in 1 of 3 patients with colorectal cancer; a Phase 2 study of this combination in V600-mutant melanoma reported an ORR of 52.4% (22/42), including 5 CRs, median PFS of 9.2 months, and median OS of 19.4 months[324].

Niraparib

Assay findings association

ATM
Q2942fs*10

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[48-50,325] , colorectal cancer[52], breast cancer[52], gastric cancer[51], cholangiocarcinoma[54], and papillary renal cell carcinoma[53].

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of glioma are limited (PubMed, Mar 2022). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[326]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[327]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[328].

Olaparib

Assay findings association

ATM
Q2942fs*10

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[48-50,325] , colorectal cancer[52], breast cancer[52], gastric cancer[51], cholangiocarcinoma[54], and papillary renal cell carcinoma[53].

SUPPORTING DATA

A Phase 1 study of olaparib in combination with temozolomide for the treatment of patients with relapsed glioblastoma reported a 6-month PFS rate of 46% (6/13)[329]. An additional case study reported a durable response (>2 years) to combination olaparib and temozolomide in a pediatric patient with glioblastoma[330]. Olaparib has been studied primarily for the treatment of ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[331-332] ; higher response rates have also been observed for patients with platinum-sensitive versus platinum-resistant cancer[332-335] . As maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib has demonstrated significantly improved median PFS and median OS compared with placebo in the Phase 3 SOLO-1 study[336] and in multiple later-phase studies[337-340] . Phase 3 studies of olaparib for patients with BRCA-mutated metastatic breast[341] or pancreatic cancer[342] or for patients with metastatic castration-resistant prostate cancer and BRCA or ATM alterations[343] have also reported significantly longer median PFS compared with chemotherapy, placebo, or hormone therapy. Additionally, olaparib has demonstrated clinical activity for patients with other solid tumors harboring BRCA mutations, including leiomyosarcoma[344], cholangiocarcinoma[345], and bladder cancer[346] in smaller studies. Olaparib in combination with the AKT inhibitor capivasertib has demonstrated clinical benefit for patients with solid tumors; a Phase 1 trial reported a 45% (25/56) DCR, including 14 PRs and 11 SDs, and 14 of those experiencing clinical benefit had germline BRCA1/2 mutated-solid tumors[347].

Rucaparib

Assay findings association

ATM
Q2942fs*10

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[48-50,325] , colorectal cancer[52], breast cancer[52], gastric cancer[51], cholangiocarcinoma[54], and papillary renal cell carcinoma[53].

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of glioma are limited (PubMed, Mar 2022). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[348]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[349]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[350]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[351]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[352]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[353]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[354]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[355].

Selumetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence demonstrating the efficacy of selumetinib in patients with BRAF V600-mutated papillary thyroid cancer[356], melanoma,[357-361] and low grade glioma[100], as well as in patients with BRAF fusion-positive glioma[100,362] , BRAF activating alterations may predict sensitivity to selumetinib.

SUPPORTING DATA

Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG[100]; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG[362]. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset[363]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[364-366] and a Phase 1 study[367]. Phase 2 studies reported clinical responses in low-grade glioma[100,362] , melanoma[357,359-361,368] , and in lung[369-371] and endometrial cancer[372]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[363]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[373]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[374]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[375], docetaxel or dacarbazine[376], AKT inhibitors[377], or cixutumumab (an anti-IGF-1R antibody)[378] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Talazoparib

Assay findings association

ATM
Q2942fs*10

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[48-50,325] , colorectal cancer[52], breast cancer[52], gastric cancer[51], cholangiocarcinoma[54], and papillary renal cell carcinoma[53].

SUPPORTING DATA

A phase 1/2 study of talazoparib with temozolomide reported 1 PR and 2 SD for patients with malignant glioma (n=8) and 2 SD for patients with astrocytoma (n=3)[379]. Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[380-381] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[52]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[382-385] .

Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating BRAF alterations may predict sensitivity to MEK inhibitors such as trametinib. Significant clinical responses to trametinib have been achieved by patients with melanoma harboring BRAF V600E[386-387], V600K[386], V600R[387], K601E[387-388], L597V[386], L597Q[388-389], or L597S[390] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[150]; as well as by patients with tumors harboring BRAF fusions[310,391-396].

SUPPORTING DATA

A study of four pediatric patients with BRAF mutation-positive non-operable astrocytoma reported a reduction in tumor volume in response to trametinib for the 3 optic gliomas with BRAF duplication[397-398]. A patient with pilocytic astrocytoma harboring an NFIA-RAF1 fusion that had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[399]. 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[400], 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[401].

Vemurafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and is FDA approved to treat melanoma as monotherapy for patients with the BRAF V600E mutation. It is also approved to treat patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data, BRAF V600E mutations may confer sensitivity to V600-targeted therapies such as vemurafenib[98-99,141-142,147,402-406].

SUPPORTING DATA

In the Phase 2 VE-BASKET study, an ORR of 25% (6/24) was reported for patients with BRAF V600-mutated gliomas, with a CR lasting 25.9 months for a patient with pleomorphic xanthoastrocytoma (PXA) and PRs reported for patients with PXA, anaplastic ganglioma, juvenile piliocytic astrocytoma, and low-grade glioma[98-99]. Other studies have reported antitumor activity of vemurafenib for patients with BRAF V600E-mutated PXA[407], glioblastoma[408], or ganglioglioma[409]. Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[138,140-149,291]. Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[141,296]. In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[410].

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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and cobimetinib is a MEK inhibitor. The combination is FDA approved to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma and colorectal carcinoma, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as vemurafenib and cobimetinib[411-413] .

SUPPORTING DATA

Clinical data on the efficacy of vemurafenib combined with cobimetinib for the treatment of CNS tumors are limited (PubMed, Oct 2021). The combination of vemurafenib and cobimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[413-415] and has been studied primarily in the context of BRAF V600-mutated melanoma, where patients treated with this combination achieved greater PFS and OS compared with vemurafenib alone[411-412,416] . Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[141,296] . In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[410].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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NOTE 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. 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 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. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
ATM

ALTERATION
Q2942fs*10

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

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Hangzhou (China), Nanjing (China), Wuhan (China), Xi'an (China), Osaka (Japan), Beijing (China), Hirakata-shi (Japan), Takatsuki-shi (Japan), Chengdu (China), Chuo-ku (Japan)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

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

NCT03742895

PHASE 2

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

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Darlinghurst (Australia), Moscow (Russian Federation), Krasnogorsk (Russian Federation)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04614909

PHASE NULL

Phase 0/2 Study of Pamiparib in Newly Diagnosed and rGBM

TARGETS
PARP

LOCATIONS: Arizona

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)

GENE
BRAF

ALTERATION
V600E

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Limited clinical and preclinical studies indicate BRAF mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

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)

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)

NCT04391595

PHASE NULL

LY3214996 Plus Abemaciclib in Recurrent Glioblastoma Patients

TARGETS
CDK4, CDK6, ERK1, ERK2

LOCATIONS: Arizona

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), California, Texas

NCT03973918

PHASE 2

Study of Binimetinib With Encorafenib in Adults With Recurrent BRAF V600-Mutated HGG

TARGETS
BRAF, MEK

LOCATIONS: California, Michigan, Pennsylvania, Maryland, North Carolina, Alabama

NCT01989585

PHASE 1/2

Dabrafenib, Trametinib, and Navitoclax in Treating Patients With BRAF Mutant Melanoma or Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
BCL2, BCL-XL, BCL-W, BRAF, MEK

LOCATIONS: California, Kansas, Missouri

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT02428712

PHASE 1/2

A Study of PLX8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors

TARGETS
BRAF, CRAF

LOCATIONS: Arizona, New York, Texas, Florida

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.

FGFR2
rearrangement

FGFR4
V109I

KDM5C
K289E

KMT2A (MLL)
A53V

MEN1
A528T

MSH3
A58V

MSH6
V215I

NOTCH1
Q1134R

PAX5
A387T

TEK
loss

Electronically signed by Erik Williams, M.D. | 18 March 2022
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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APPENDIX Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*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*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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FoundationOne 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. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

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. 2022. 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.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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 >10%, 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, CBL, 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.

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 CDx.

TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, 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

MR Suite Version 6.1.0

The median exon coverage for this sample is 1,018x

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