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 Yao, Cheng-Chu
DATE OF BIRTH 13 March 1957
SEX Male
MEDICAL RECORD # 22833530

PHYSICIAN

ORDERING PHYSICIAN Hsu, Pin-Chuan
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Brain
SPECIMEN ID S110-22115 A (PF21003)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 03 August 2021
SPECIMEN RECEIVED 24 August 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

BRCA1 rearrangement intron 2, rearrangement intron 19
EGFR amplification, EGFRvIII
ALOX12B R469W
CDKN2A/B CDKN2A loss exon 1
FLT3 V592I

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

6 Therapies with Clinical Benefit
0 Therapies with Lack of Response
19 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
BRCA1 - rearrangement intron 2, rearrangement intron 19	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials *see p. 11*		
EGFR - amplification, EGFRvIII	none	Cetuximab
		Panitumumab
9 Trials *see p. 13*		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS 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.

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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

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
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

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
BRCA1

ALTERATION
rearrangement intron 2, rearrangement intron 19

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[47-64] or ATR inhibitors[65-67]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[48,53,56,63-64] and for patients with platinum-resistant or -refractory disease[47,52,59,62]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD[65]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[66]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[68]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[69]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[70], ovarian carcinoma[71], and TNBC[72] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. In a Phase 1 monotherapy trial of the WEE1 inhibitor adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[73]. Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[74-83].

FREQUENCY & PROGNOSIS

BRCA1 mutations have been reported in 1% of glioblastoma cases analyzed[84]. Multiple cases of glioblastoma in patients with germline BRCA1 mutation and prior history of breast cancer have been described[85-87]. A germline BRCA1 mutation has also been reported in a patient with oligodendroglioma[88]. One study reported that presence of BRCA mutations was associated with significantly shorter OS in male patients with glioma; among patients with BRCA-mutant tumors, there was no difference in OS among those with BRCA1 mutations, BRCA2 mutations, or both[89].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[90]. Alterations such as seen here may disrupt BRCA1 function or expression[91-93].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[94-95], and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[96]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[97]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[96,98-103]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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GENE
EGFR

ALTERATION
amplification, EGFRvIII

POTENTIAL TREATMENT STRATEGIES

Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[104-108]; however, a small subset of patients has experienced clinical benefit[104-106]. The second-generation EGFR TKIs afatinib and dacomitinib have shown minimal efficacy for patients with EGFRvIII glioblastoma (GBM)[104,106-107,109]. A Phase 1/2 study of afatinib, temozolomide, or the combination for patients with GBM reported clinical benefit, including for patients with EGFRvIII; however, temozolomide alone and in combination exhibited better responses than afatinib monotherapy[107,109]. A Phase 2 trial of dacomitinib for patients with EGFR-amplified GBM reported a DCR of 26% (5/19) among patients with EGFR amplification and EGFRvIII; however, the trial failed to meet its primary endpoint of 6-month PFS[104]. A retrospective biomarker analysis of another Phase 2 study of dacomitinib for patients with GBM found no association between EGFRvIII and clinical benefit[106]. A Phase 1 trial of ABT-414, an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with GBM reported 2 complete responses (CR) and 5 partial responses (PR) in 18 patients with EGFR amplification (39% response rate); no CR or PR were observed in 28 patients without EGFR amplification[110]. A clinical study of patients with GBM treated with gefitinib or erlotinib found no correlation between EGFR amplification or mutation and response to the therapy, but sensitivity to EGFR kinase inhibitors was associated with the co-expression of the EGFRvIII alteration and PTEN[111]. Activation of multiple ERBB family receptors or activation of the PI3K pathway may be responsible for resistance to EGFR-targeted therapy in GBM; therefore, inhibition of ERBB family members or treatment with PI3K/AKT inhibitors or mTOR inhibitors such as everolimus or temsirolimus in combination with an EGFR-targeted treatment, may be a therapeutic option[112-113]. In multiple glioblastoma studies, the presence of EGFRvIII has not predicted clinical benefit from erlotinib or gefitinib[114-118]. In a retrospective study of patients with glioblastoma treated with erlotinib or gefitinib, co-expression of EGFRvIII with PTEN protein was the strongest predictor of response (P<0.001)[111], suggesting that activity in this setting is dependent on PTEN status[119]. However, a prospective Phase 2 trial testing erlotinib monotherapy for patients with EGFRvIII and PTEN-positive recurrent glioblastoma reported minimal efficacy and was terminated[118]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[111,120-122]. Case studies of patients with cancers harboring EGFR rearrangements treated with osimertinib have reported mixed results. Of 3 patients with non-small cell lung cancer (NSCLC) with EGFR kinase domain duplication (KDD), 2 attained PRs with osimertinib, whereas the third experienced PD[123]. A patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFRvIII, experienced progression of the EGFRvIII-positive tumor during treatment with osimertinib[124]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[125-126]. EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[127-130], panitumumab[128], or necitumumab[131]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[132-133] that has also shown benefit in patients with CRC and melanoma[134-135]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[136-139]. Preclinical studies have reported that EGFR-mutant cells[136-138], including cells with exon 20 insertions[140], are sensitive to HSP90 inhibitors. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[141-142]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[143]. The reovirus Reolysin targets cells with activated RAS signaling[144-146] and is in clinical trials for patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[147-155]. Novel approaches that specifically target EGFRvIII, such as the vaccine rindopepimut, are under investigation in both clinical and preclinical studies. Phase 2 studies of rindopepimut reported promising results, with increases in median overall survival (OS) for patients with newly diagnosed EGFRvIII-positive GBM treated with rindopepimut in combination with temozolomide compared to temozolomide alone after resection and chemoradiation (25 vs. 15-16 months)[156], as well as for patients with bevacizumab-naïve relapsed EGFRvIII-positive GBM treated with rindopepimut in combination with bevacizumab compared to bevacizumab alone (12 vs. 8 months)[157]. However, a Phase 3 study of rindopepimut combined with temozolomide compared to control in newly diagnosed resected EGFRvIII-positive GBM after chemoradiation was terminated after the second interim analysis, due to a lack of clinical benefit as measured by OS (20.1 vs. 20.0 months)[158].

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas[84,159-161]. Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)[84,159-161]. In the glioblastoma (GBM) TCGA dataset, putative high-level amplification of EGFR has been found in 48% of cases and mutation has been found in 21% of cases[84]. Missense mutations in the EGFR extracellular domain have been found in 10-15% of GBMs and approximately half have a low-level amplification of the mutated allele[162-163]. One study detected EGFR alterations in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[164]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[111,165-172]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[173-174]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[175]. The link between EGFRvIII status and prognosis is unclear, although some studies

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suggest that it may be linked to improved survival and response to chemotherapy[176].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[177]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[178-180]. A mutation of the EGFR gene, referred to as EGFRvIII, results from a gene rearrangement that deletes exons 2-7. This alteration causes an in-frame deletion of 801 base pairs encoding part of the extracellular ligand-binding domain[165]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[165,181].

GENE

ALOX12B

ALTERATION
R469W

TRANSCRIPT ID
NM_001139

CODING SEQUENCE EFFECT
1405C>T

VARIANT ALLELE FREQUENCY (% VAF)
37.0%

POTENTIAL TREATMENT STRATEGIES

There are no therapies or clinical trials targeting alterations in ALOX12B.

FREQUENCY & PROGNOSIS

In the MSK-IMPACT pan-cancer dataset, ALOX12B mutation and amplification have been reported in 0.8% and 0.1% of more than 10,000 samples across 62 solid tumor types analyzed, respectively[182]. The implications of ALOX12B alterations for cancer prognosis have not been evaluated in published studies (PubMed, 2021).

FINDING SUMMARY

ALOX12B encodes the epidermal lipoxygenases 12R-lipoxygenase (12R-LOX). 12R-LOX regulates water evaporation through epithelial cells[183]. Loss-of-function mutations in ALOX12B have been reported in autosomal recessive congenital ichthyosis[183]. In one study, amplification of the locus encompassing ALOX12B/ALOX15B correlated with lower immune cytolytic activity in tumor cells[184].

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GENE
CDKN2A/B

ALTERATION
CDKN2A loss exon 1

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[185-188]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[189-190], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[191-197]; 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[198-199], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS
Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[160] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[84] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2020)[200-201]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[171,202-203]. 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[204]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[164]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[205]. 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[202,206]. 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[207-208].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[209-210]. 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[211-212]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[213-214]. One or more alterations observed here are predicted to result in p16INK4a loss of function[215-236]. One or more alterations seen here are predicted to result in p14ARF loss of function[219,236-239].

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[240]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[241-242]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[243-245]. 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[246-248]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
FLT3

ALTERATION
V592I

TRANSCRIPT ID
NM_004119

CODING SEQUENCE EFFECT
1774G>A

VARIANT ALLELE FREQUENCY (% VAF)
46.7%

POTENTIAL TREATMENT STRATEGIES
Therapies targeting FLT3 are under clinical investigation, including crenolanib, gilteritinib, lestaurtinib, midostaurin, pexidartinib, ponatinib, quizartinib, sorafenib, and sunitinib. The TKIs midostaurin[249-252] and gilteritinib[253-255] have shown significant clinical activity for patients with relapsed/refractory AML and FLT3-ITD or FLT3-TKD mutations and are approved for these patient populations.

FREQUENCY & PROGNOSIS
FLT3 mutation has been detected in about 1.0% of glioma and glioblastoma cases (COSMIC, Feb 2021)[256-258]. One study reported FLT3 mRNA expression in 14/14 glioblastoma samples analyzed[259]. In another study, FLT3 mRNA expression was not reported in any of five glioblastoma cell lines analyzed[260]. One study of glioma reported reduced OS (HR=19.46, p<0.0001) for patients with FLT3 mutation compared to those without[258].

FINDING SUMMARY
FLT3 encodes a receptor tyrosine kinase that potentiates signaling through the RAS and PI3K pathways[261-263]. FLT3 alterations, such as observed here, are predicted to be activating and oncogenic[264-276]. In preclinical studies, the activating FLT3 mutations S451F, Y572C, V579A, F590G_Y591D, V592A, V592G, F594L, and R834Q conferred sensitivity to midostaurin[264,266,271].

Cetuximab

Assay findings association

EGFR
amplification, EGFRvIII

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[128].

SUPPORTING DATA

A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[277]. In preclinical trials, cetuximab, matuzumab, and panitumumab were reported to be ineffective at blocking EGFR dimerization and activation in GBM cells expressing EGFR extracellular domain mutations[278]. However, another study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better progression-free survival (PFS) and numerical (although not statistically significant) improvement in overall survival (OS)[172].

Niraparib

Assay findings association

BRCA1
rearrangement intron 2,
rearrangement intron 19

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

On the basis of clinical evidence in ovarian and breast cancers[51-52,279] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of glioma are limited (PubMed, Apr 2021). 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)[51]. 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[52]. 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)[280].

Olaparib

Assay findings association

BRCA1
rearrangement intron 2,
rearrangement intron 19

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

On the basis of extensive clinical evidence in ovarian cancer[57-61] as well as strong clinical evidence in multiple other cancer types[47-49,57,60,64,281] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

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)[282]. An additional case study reported a durable response (>2 years) to combination olaparib and temozolomide in a pediatric patient with glioblastoma[283]. 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[57,60] ; higher response rates have also been observed for patients with platinum-sensitive versus platinum-resistant cancer[59-60,62,284] . 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[63] and in multiple later-phase studies[55-56,285-286] . Phase 3 studies of olaparib for patients with BRCA-mutated metastatic breast[50] or pancreatic cancer[64] or for patients with metastatic castration-resistant prostate cancer and BRCA or ATM alterations[287] 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[288], cholangiocarcinoma[289], and bladder cancer[290] 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[291]. In a Phase 2 study of olaparib plus pembrolizumab for patients with advanced solid tumors, those with BRCA1 or BRCA2 mutations and those with homologous recombination deficient tumors reported the highest ORRs of 29% (6/21) and 21% (16/76), respectively. Patients with homologous recombination repair deficient tumors, including and excluding patients with BRCA1/2 mutations, reported lower ORRs of 15% (8/53) and 6.3% (2/32), respectively[292].

Panitumumab

Assay findings association

EGFR
amplification, EGFRvIII

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[128].

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs[293]. Two Phase 2 studies of panitumumab and chemotherapy in biliary tract cancer, including cholangiocarcinoma, reported encouraging efficacy and manageable toxicity[294-295] . In a Phase 2 trial of advanced NSCLC, the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[296]. A Phase 1 study of panitumumab for patients with metastatic renal cell carcinoma resulted in a response rate of 6% and stable disease in 50% of patients[297].

Rucaparib

Assay findings association

BRCA1
rearrangement intron 2,
rearrangement intron 19

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

On the basis of strong clinical evidence in ovarian cancer[53-54,298] , as well as clinical data in other cancer types[54,299-300] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of glioma are limited (PubMed, Apr 2021). 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[53]. 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[298]. 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[54]. 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[299]. 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[300]. 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[301]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[302]. 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[303].

Talazoparib

Assay findings association

BRCA1
rearrangement intron 2,
rearrangement intron 19

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

On the basis of strong clinical data in breast cancer[304-306] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[307-310] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of glioma are limited (PubMed, May 2021). 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[305-306] . 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[311]. 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[307-309,312] .

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.

Electronically signed by Brennan Decker, M.D., Ph.D. | 31 August 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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
BRCA1

ALTERATION
rearrangement intron 2, rearrangement intron 19

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (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), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

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)

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT03188965

PHASE 1

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

TARGETS
ATR

LOCATIONS: Sunto (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore), St. Gallen (Switzerland), Bellinzona (Switzerland), Newcastle Upon Tyne (United Kingdom), Genève (Switzerland), Sutton (United Kingdom), Edmonton (Canada)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (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)

GENE
EGFR

ALTERATION
amplification, EGFRvIII

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03618667

PHASE 2

GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT03829436

PHASE 1

TPST-1120 as Monotherapy and in Combination With (Nivolumab, Docetaxel or Cetuximab) in Subjects With Advanced Cancers

TARGETS
PD-1, PPARalpha, EGFR

LOCATIONS: California, Michigan, Oklahoma, Pennsylvania, New York, Tennessee, Maryland, North Carolina, Florida

NCT04172597

PHASE 2

A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

NCT02800486

PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbitux) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS
EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

Super-selective Intra-arterial Repeated Infusion of Cetuximab for the Treatment of Newly Diagnosed Glioblastoma

TARGETS
EGFR

LOCATIONS: New York

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), California, Colorado, Arizona, Toronto (Canada), Oklahoma, Texas, Pennsylvania

NCT02451553

PHASE 1

Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Washington

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT02303678

PHASE 1

D2C7 for Adult Patients With Recurrent Malignant Glioma

TARGETS
EGFRvIII

LOCATIONS: North Carolina

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.

BRIP1
R814C

CCNE1
D224H

CDC73
F250L

CSF3R
Q96P

EP300
A2289T

FGF6
P197L

FUBP1
I382T

GABRA6
R46W

PALB2
T1012I and V425M

PARP3
A235V and H146Y

PTCH1
K353R

ROS1
T1107A

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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*	*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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. 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.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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.

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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%.

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

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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 4.2.0

The median exon coverage for this sample is 637x

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