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)

DATE OF BIRTH 10 November 1990
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Brain
SPECIMEN ID Q35284-2D
SPECIMEN TYPE Block
DATE OF COLLECTION 07 November 2020
SPECIMEN RECEIVED 09 January 2021

Biomarker Findings

Microsatellite status - Cannot Be Determined
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

BRAF V600E - subclonal†
EGFR kinase domain duplication
IDH1 R132H
PIK3CA H1047R - subclonal†
ATRX R808*
TP53 H179Q

1 Disease relevant genes with no reportable alterations: ***PDGFRA***

† See About the Test in appendix for details.

16 Therapies with Clinical Benefit
0 Therapies with Lack of Response
35 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - Cannot Be Determined	**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 BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
BRAF - V600E - subclonal	none	Regorafenib 2A
		Dabrafenib
		Dabrafenib + Trametinib
		Encorafenib + Binimetinib
		Selumetinib
		Trametinib
		Vemurafenib
10 Trials *see p. 17*		Vemurafenib + Cobimetinib
EGFR - kinase domain duplication	none	Afatinib
		Dacomitinib
		Erlotinib
		Gefitinib
6 Trials *see p. 19*		Osimertinib
IDH1 - R132H	none	Ivosidenib
9 Trials *see p. 20*		
PIK3CA - H1047R - subclonal	none	Everolimus
10 Trials *see p. 22*		Temsirolimus

☐ *NCCN category*

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.

ATRX - R808* ..... p. 8 ***TP53*** - H179Q ..... p. 9

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
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[12-14]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[12], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[15]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[12], in GBMs with a previous lower grade astrocytoma[13], and in giant cell GBM compared to classic GBM[14].

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[16]. 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[16-18]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[16], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[19]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[19-21] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[22-24]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
0 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[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-33]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[25,34-35]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[36-37] or anti-PD-L1[38] 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)[39]. 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[40-41]. Increased TMB has been reported to correlate with higher tumor grade in glioma[42] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[36], as well as with shorter OS of patients with diffuse glioma[43].

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[44-45] and cigarette smoke in lung cancer[11,46], treatment with temozolomide-based chemotherapy in glioma[47-48], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[49-53], and microsatellite instability (MSI)[49,52-53]. 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[25,34-38].

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GENE
BRAF

ALTERATION
V600E - subclonal

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

VARIANT ALLELE FREQUENCY (% VAF)
2.3%

POTENTIAL TREATMENT STRATEGIES

BRAF V600 mutations activate MEK-ERK signaling and are associated with sensitivity to BRAF V600 mutant–specific inhibitors such as vemurafenib[54], dabrafenib[55], and encorafenib[56]; the combination of BRAF V600-mutant-selective inhibitors with MEK inhibitors such as encorafenib plus binimetinib[57], vemurafenib plus cobimetinib[58-59], or dabrafenib plus trametinib[60-62]; MEK inhibitors such as trametinib[63-65], cobimetinib[66], binimetinib[67], and selumetinib[68-70]; multikinase inhibitors that have activity against BRAF such as regorafenib[71-72]; and ERK inhibitors[73]. A Phase 2 trial of selumetinib reported partial response (PR) in 32% (8/25) of pediatric patients with BRAF-mutant pilocytic astrocytoma, including 2 with BRAF V600E and 6 with a KIAA1549-BRAF fusion[69]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs in 3/19 previously treated and 1/2 newly diagnosed patients with BRAF V600E-mutant melanoma, 3/12 patients with BRAF-mutant lung cancer (2 with V600E and 1 with L597Q), and 4/21 patients with other BRAF-mutant cancers (2 with G469A, 1 with V600E, and 1 with L485W); 2 patients with BRAF V600E mutations also experienced CNS response[74]. BRAF inhibitors can induce adverse effects such as the development of cutaneous squamous cell carcinomas (SCC), keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[54-55,75]. Meta-analysis confirmed a reduced risk of developing cutaneous SCC with combined BRAF- and MEK-inhibition relative to BRAF-inhibitor monotherapy[76]. A Phase 1/2 trial of PLX8394, a next-generation BRAF inhibitor predicted to not induce paradoxical MAPK pathway activation[77-78], reported PRs in patients with BRAF V600E-mutant tumors, specifically in glioma (3/4), papillary thyroid carcinoma (1/9), colorectal cancer (1/10), and ovarian cancer (1/1)[79].

FREQUENCY & PROGNOSIS

BRAF V600E has been reported in 0.6-6% of GBM samples[80-84], with one study reporting BRAF V600E in 54% (7/13) of epithelioid glioblastomas[85]. 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[83,86-88]. In various studies, BRAF alterations have been reported in 1-3% of gliomas including low grade gliomas[47,80-82,84,89] and glioblastomas (GBM)[90]. 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[80,82,91], and the frequency of the BRAF V600E mutation in astrocytoma reported in the literature varies by cohort[92-94]. BRAF V600E is not strongly associated with prognosis in patients with astrocytoma[92,94]. While one study associated KIAA1549-BRAF fusion with improved prognosis in pediatric patients with low grade astrocytomas[95], others reported no significant association between BRAF rearrangements and outcome[96-99].

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[100-101]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[102-103]. 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[102,104-105]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[102,106]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[54-55,105,107-115]; other mutations at this position are predicted to behave similarly.

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GENE
EGFR

ALTERATION
kinase domain duplication

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[116], gefitinib[117], afatinib[118], dacomitinib[119], and osimertinib[120]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[120-121]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[122-123] that has also shown benefit in patients with CRC and melanoma[124-125]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[126-129]. Preclinical studies have reported that EGFR-mutant cells[126-128], including cells with exon 20 insertions[130], 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[131-132]. 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[133]. The reovirus Reolysin targets cells with activated RAS signaling[134-136] and is in clinical trials in 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[137-145]. 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[146]. 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[147]. 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[148-149].

FREQUENCY & PROGNOSIS

In the TCGA datasets, EGFR alterations have been reported in 25% of gliomas, and are more frequently detected in glioblastoma (54%) than in lower grade gliomas (9%)[90,150-151]. In the glioblastoma TCGA dataset, putative high-level amplification of EGFR has been found in 48% of cases, and mutation has been found in 21% of cases[90]. 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[152-153]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[154-155]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[156].

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[157]. The EGFR rearrangement seen here is an EGFR kinase domain duplication (EGFR-KDD). EGFR-KDDs, including in-frame tandem duplications of exons 18-25 or exons 18-26, have been shown to be activating and oncogenic[158-161]. Other EGFR-KDD alterations, such as duplication of exons 17-25 or exons 14-26, have been observed in patients with lung adenocarcinoma or lung squamous cell carcinoma, respectively[162]. A patient with lung adenocarcinoma with an EGFR exon 18-25 duplication had a PR to afatinib[158].

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GENE
IDH1

ALTERATION
R132H

TRANSCRIPT ID
NM_005896

CODING SEQUENCE EFFECT
395G>A

VARIANT ALLELE FREQUENCY (% VAF)
37.6%

POTENTIAL TREATMENT STRATEGIES

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[163]. A Phase 1b/2 study of the IDH1 inhibitor olutasidenib for patients with IDH1-mutated glioma reported a DCR of 50% (n=24) with 1 PR[164]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18.2% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[165]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[166-169]. In a Phase 1 trial of the PD-L1 inhibitor atezolizumab in patients with glioblastoma (GBM), 2 of the 3 patients with IDH1-mutant tumors experienced clinical benefit (1 PR and 1 long-term SD; the third patient experienced short-term SD), whereas none of the 8 patients with IDH1-wild-type GBM experienced benefit (8/8 PD); significantly longer PFS and a trend toward longer OS were observed in the patients with IDH1-mutated tumors compared to the patients with IDH1-wild-type tumors[38]. Preclinical data indicate that IDH1-mutated glioma may be sensitive to the glutaminase inhibitor telaglenastat in combination with radiotherapy[170].

FREQUENCY & PROGNOSIS

IDH1 mutation is characteristic of low-grade gliomas and secondary glioblastoma, and is relatively rare in primary glioblastoma[171-175]. In the TCGA datasets, IDH1 mutation has been found in 77% of lower grade glioma cases and in 5% of glioblastoma cases[89-90]. Several studies have found IDH1 mutations to be associated with improved prognosis and longer PFS and OS in patients with various types of glioma including anaplastic astrocytoma and GBM[175-182].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[183]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[183-187]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[185-189], which promotes tumorigenesis[185,190-193].

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GENE
PIK3CA

ALTERATION
H1047R - subclonal

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
3140A>G

VARIANT ALLELE FREQUENCY (% VAF)
7.7%

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT[194-195]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[196-201]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 SDs)[202]. A patient with previously treated HER2-negative metastatic breast cancer harboring a PIK3CA H1047R alteration achieved an exceptional response with the pan-class I PI3K inhibitor copanlisib[203]. However, studies of copanlisib and the pan-class I PI3K inhibitor buparlisib have demonstrated limited efficacy against PIK3CA-mutated tumors[204-210]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[195]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but high DCRs (55% [36/55] to 58% [64/111])[211]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[212]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[213]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[214]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[215-219].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma samples analyzed in the TCGA dataset[90], and other studies report the incidence of PIK3CA mutations in primary glioblastomas as 5-18%[220-222]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[151,220-223]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[222]. Although the effects of PIK3CA alterations on prognosis in gliomas has not been directly studied (PubMed, Feb 2020), activated PI3K signaling has been shown to be associated with poor outcome in GBM patients[224].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[225-226]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[227-246].

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GENE
ATRX

ALTERATION
R808*

TRANSCRIPT ID
NM_000489

CODING SEQUENCE EFFECT
2422C>T

VARIANT ALLELE FREQUENCY (% VAF)
44.9%

POTENTIAL TREATMENT STRATEGIES

No targeted therapies are available to address ATRX inactivation. Although ATR inhibition is being investigated as a potential therapeutic approach in the context of ALT, a preclinical study demonstrated that ATRX inactivation is not sufficient to confer sensitivity to ATR inhibitors[247]. However, ATRX-deficient GBM cells were sensitive to the double-strand break-inducing agents doxorubicin, irinotecan, and topotecan but not single-strand break-inducing agents such as temozolomide[248]. Preclinical evidence suggests that ATRX may be required for CDK4/6 inhibitors to be most effective[249].

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[250]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[250-252], 12.6% of pheochromocytomas and paragangliomas[253], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[254-258]. ATRX loss in PNET[251,259] and melanoma[260] and mutation in other neuroendocrine tumors[253] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[248]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[261-264] and has been proposed as a distinguishing biomarker[262-264]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[255-258]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[262]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[265-266].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[267-268]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[250,266,269-270]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[271-273]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[247,267]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[274].

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GENE
TP53

ALTERATION
H179Q

TRANSCRIPT ID
NM_000546

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POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[275-278], or p53 gene therapy and immunotherapeutics such as SGT-53[279-283] and ALT-801[284]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[285]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[286]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[287]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[288]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[289]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[290]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[283]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[291]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[292-294]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[295]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[296-297]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[298-299]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[151,300]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[301-306]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with GBM[307]. 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[308-313]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[308-309]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[314]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[312,315-316]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[317].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[318]. Alterations such as seen here may disrupt TP53 function or expression[319-323]. One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Sep 2020)[324]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[325-327], including sarcomas[328-329]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[330] to 1:20,000[329]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[331]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Afatinib

Assay findings association

EGFR
kinase domain duplication

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. Extensive clinical evidence has demonstrated that treatment with afatinib, when compared with chemotherapy, increases PFS for patients with EGFR-mutated NSCLC[118,332] . In a Phase 3b trial, first-line afatinib enabled an ORR and DCR of 45.9% (220/479) and 86.0% (412/479), respectively, for patients with EGFR-mutated NSCLC[333]. One patient with lung adenocarcinoma and the EGFR-KDD alteration achieved a PR of 4 months with gefitinib treatment followed by afatinib and osimertinib[334]. A patient with lung adenocarcinoma and an EGFR kinase domain duplication experienced a PR to afatinib, but later developed a co-occurring EGFR amplification[158].

SUPPORTING DATA

A Phase 2 clinical trial of afatinib, temozolomide, and both in combination for patients with glioblastoma (GBM) reported partial responses and stable disease achievement, including in patients with EGFRvIII, although temozolomide alone and in combination exhibited better responses than afatinib monotherapy in this study[335]. A case study reported a patient with recurrent GBM harboring various EGFR alterations (including amplification, EGFRvIII, and multiple missense mutations) who achieved prolonged response and survival of >5 years subsequent to treatment with afatinib plus temozolomide[336]. Afatinib has shown a lack of efficacy in several patients with GBM harboring EGFR amplification or activating mutations[337].

Dabrafenib

Assay findings association

BRAF
V600E - subclonal

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[54-55,105,107-114,338] ; 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[54-55,105,107-114,338] . A Phase 1/2 study evaluating single-agent dabrafenib for the treatment of pediatric patients with BRAF V600-mutant gliomas reported an ORR of 44% (14/32; 1 CR, 13 PR), median duration of response of 25.6 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[339-340] . In separate case studies, patients with previously treated BRAF V600-mutant LGGs and HGGs exhibited CRs for 3 months and >2 years, respectively, following treatment with single-agent dabrafenib[341-342] . Treatment with the combination of dabrafenib and trametinib resulted in rapid clinical improvement and radiographic responses in two adult patients with BRAF V600-mutant HGG[343]. 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)[344]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wild-type BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutant thyroid cancer[55,75,345] . 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[60,62,346-348] .

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Dabrafenib + Trametinib

Assay findings association

BRAF
V600E - subclonal

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[60-62,349-355] .

SUPPORTING DATA

Dabrafenib combined with trametinib has shown clinical efficacy for patients with BRAF V600E-mutated high-grade gliomas (HGGs). A Phase 2 open-label trial of the combination treatment for previously treated recurrent or progressive glioma with BRAF V600E mutation reported RANO ORRs for 27.1% of patients with HGGs (10/37; 1 CR)[356-357] . 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[358] and rapid clinical improvement and radiographic responses for 2 additional adult patients[343]; however, 1 patient did not respond to this regimen[359]. A patient with GBM lacking epithelioid or rhabdoid features experienced a CR from dabrafenib plus trametinib[360]. Dabrafenib plus trametinib enabled a pediatric patient with anaplastic astroblastoma to remain disease-free for 20 months[361].

Dacomitinib

Assay findings association

EGFR
kinase domain duplication

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical[119,362-363] and preclinical[364-365] data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

A Phase 2 trial of dacomitinib in patients with EGFR-amplified glioblastoma reported CR in 1/49 (2%), PRs in 2/49 (4%), and SD in 12/49 (24%) of patients, for a DCR of 15/49 (31%)[366]. Among the patients with EGFR-amplified/EGFRvIII glioblastoma, 1/19 (5%) PR and 4/19 (21%) SDs were reported, for a DCR of 5/19 (26%)[366].

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E - subclonal

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[57,367-369] , and activity in colorectal, thyroid, and lung cancer[369-371] , 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[57,369-371] , 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[57,367,372] . 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[373].

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Erlotinib

Assay findings association

EGFR
kinase domain duplication

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. In patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[374]. A heavily pretreated patient with KRAS wild-type metastatic pancreatic ductal adenocarcinoma and an EGFR exon 19 deletion experienced a sustained partial response for 32 weeks to erlotinib monotherapy[375].

SUPPORTING DATA

A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[147]. In a Phase 2 study of 65 patients with GBM or gliosarcoma, treatment with erlotinib, temozolomide, and radiotherapy resulted in longer progression-free survival relative to a historical control study utilizing a regimen of temozolomide and radiotherapy alone (19.3 months vs. 14.1 months)[376]. However, in a Phase 1/2 trial of erlotinib monotherapy in 11 patients with relapsed or refractory GBM or anaplastic astrocytoma, all patients showed disease progression and the drug showed significant toxicity[377]. In addition, a Phase 2 trial of patients with recurrent or progressive GBM treated with erlotinib and sorafenib did not meet its objective of a 30% increase in overall survival time compared with historical controls; sorafenib was found to increase erlotinib clearance[378].

Everolimus

Assay findings association

PIK3CA
H1047R - subclonal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of extensive clinical[196-197,200] and preclinical[201] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus.

SUPPORTING DATA

A Phase 2 trial of radiotherapy (RT), temozolomide (TMZ), and bevacizumab followed by everolimus and bevacizumab reported that 61% (31/51) of patients with newly diagnosed glioblastoma had objective responses with a median progression-free survival (PFS) of 11.3 months and median overall survival (OS) of 13.9 months[379]. A Phase 2 study of everolimus combined with TMZ and RT for the treatment of newly diagnosed glioblastoma reported a median PFS of 6.4 months and median OS of 15.8 months[380]. A Phase 1 trial of everolimus plus TMZ for patients with newly diagnosed or progressive glioblastoma reported partial responses (PR) in 11% (3/28) and stable disease (SD) in 57% (16/28) of cases[381]. A pilot study of everolimus with gefitinib in patients with recurrent glioblastoma reported 14% (3/22) PRs, 36% (8/22) SDs, and median PFS and OS of 2.6 months and 5.8 months, respectively[382]. Everolimus treatment achieved SD in 45% (5/11) of pediatric patients with heavily pretreated low-grade CNS tumors; median PFS of these responses was 14 months[383]. Studies have shown a lack of efficacy in several patients with glioblastoma harboring PI3K-AKT-mTOR pathway activating mutations[337,380] . 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[384], 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[385].

Gefitinib

Assay findings association

EGFR
kinase domain duplication

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[374,386-391] .

SUPPORTING DATA

A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[147]. A Phase 2 clinical study of gefitinib in patients with high-grade glioma (including GBM, anaplastic astrocytoma, and oligodendroglioma) reported 18% (5/28) disease stabilization; efficacy was not correlated with EGFR expression[392]. However, a Phase 1/2 clinical trial of gefitinib combined with radiotherapy in 178 patients with GBM reported no overall survival benefit of added gefitinib, and EGFR expression was found to be of no prognostic value for patients treated with gefitinib plus radiotherapy[393]. A Phase 2 trial of preoperative gefitinib treatment in patients with recurrent GBM reported that although EGFR phosphorylation was decreased in treated patients as compared to the control group, measurement of 12 downstream molecules revealed no significant changes[394].

Ivosidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor that is FDA approved to treat patients with relapsed or refractory acute myeloid leukemia (AML) and a susceptible IDH1 mutation. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[395] and cholangiocarcinoma[396-397] and limited clinical data in myelodysplastic syndrome (MDS)[395] and glioma[163,398] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In a Phase 1 study of ivosidenib for patients with IDH1-mutated advanced solid tumors, 1 patient achieved PR in the non-enhancing glioma population (ORR=2.9% [1/35]); for patients with non-enhancing glioma and enhancing glioma, SD rates were 85.7% (30/35) and 45.2% (14/31), respectively, and median PFS was 13.6 months and 1.4 months, respectively[163,398] .

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Osimertinib

Assay findings association

EGFR
kinase domain duplication

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib[120-121,399] . T790M-positive patients showed higher response rates than T790M-negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)[120]. In preclinical assays, cells transformed with the EGFR kinase domain duplication were sensitive to osimertinib, although one cell line with this EGFR variant was not inhibited at clinically achievable levels[158].

SUPPORTING DATA

In a case study, a patient with recurrent, bevacizumab-refractory glioblastoma (GBM) treated with osimertinib experienced near-complete resolution of one lesion harboring EGFR A289V and C628F missense mutations, but progression of a second lesion which was positive for EGFRvIII but negative for other EGFR alterations[400]. Osimertinib has been studied primarily for the treatment of EGFR-mutated NSCLC. The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (mPFS; 18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months, HR=0.80) for patients with advanced non-small cell lung cancer (NSCLC) and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[121,401] . In the Phase 3 ADAURA study, patients with early-stage EGFR-mutated NSCLC receiving adjuvant osimertinib experienced both longer disease-free survival (DFS; not reached vs. 19.6 months, HR=0.17) and central nervous system DFS (not reached vs. 48.2 months, HR=0.18) than those receiving placebo[402]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and mPFS of 2.8 months[120]. A Phase 2 study of osimertinib for EGFR-TKI-naïve patients with metastatic or recurrent NSCLC and uncommon EGFR mutations reported a 50.0% (18/36) ORR and an 88.9% (32/36) DCR with a median PFS of 8.2 months and a median duration of response of 11.2 months; patients harboring L861Q, G719X, or S768I mutations had ORRs of 77.8% (7/9), 52.6% (10/19), and 37.5% (3/8), respectively[403]. A Phase 1/2 trial of osimertinib in combination with bevacizumab for patients with untreated metastatic EGFR-mutated non-small cell lung cancer (NSCLC) reported an 80% (39/49) ORR, a 100% (6/6, 2 CRs) central nervous system response rate, median PFS of 19 months, and a 1-year PFS rate of 72%[404]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[405].

Regorafenib

Assay findings association

BRAF
V600E - subclonal

AREAS OF THERAPEUTIC USE

Regorafenib is a small-molecule inhibitor of multiple kinases, including RET, VEGFRs, PDGFRs, KIT, and RAF family proteins. It is FDA approved to treat hepatocellular carcinoma that has been previously treated with sorafenib, metastatic colorectal cancer (CRC), or advanced gastrointestinal stromal tumors (GISTs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Alterations that activate BRAF may predict sensitivity to regorafenib. Regorafenib as a monotherapy[71-72] , or in combination with panitumumab[71], was reported to provide clinical benefit for 2 patients with BRAF V600E-mutant CRC[71-72,406] . Furthermore, a patient with an acinic cell tumor of the parotid gland harboring a duplication of the BRAF kinase domain achieved a partial response to regorafenib monotherapy, which was ongoing after 12 months of treatment[407].

SUPPORTING DATA

A Phase 1 study of regorafenib in combination with the anti-EGFR antibody cetuximab included one patient with glioblastoma, who derived prolonged stable disease (SD) from this combination and was found to have an EGFR variant[408]. A Phase 1 trial of regorafenib for 41 pediatric patients with genomically unselected recurrent or refractory solid tumors, including 20 patients with central nervous system tumors, reported SD of at least 15 weeks for 8 patients, with 2 anaplastic ependymoma cases experiencing SD for 31 weeks as well as more than 56 weeks. The trial observed tolerable toxicity consistent with that in adult patients and noted increased hematologic toxicity in heavily pretreated patients[409].

Selumetinib

Assay findings association

BRAF
V600E - subclonal

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[410], melanoma,[70,411-414] and low grade glioma[69], BRAF activating alterations may predict sensitivity to selumetinib.

SUPPORTING DATA

Clinical data on the efficacy of selumetinib for the treatment of glioblastoma are limited (PubMed, Oct 2020). Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[415-416] and a Phase 1 study[417]. Phase 2 studies reported clinical responses in low-grade glioma[68-69] , melanoma[70,411,413-414,418] , lung[419-420] and endometrial cancer[421]. Phase 1 studies for selumetinib in solid tumors resulted in 1/15 PR (CRC) and 5/15 SD reported from patients with tonsil SCC, NSCLC, and CRC[422], and achieved 2/39 PR (CRC) and 18/39 SD in combination with cyclosporin A[423]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[424], docetaxel or dacarbazine[425], AKT inhibitors[426], and cixutumumab (anti-IGF-1R antibody)[427] reported clinical responses in patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer. Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 9/25 PR for patients with BRAF alterations and 10/25 PR for those with NF1-associated LGG[69] and a Phase 1 study for selumetinib reported 5/25 PR for LGG patients[68].

Temsirolimus

Assay findings association

PIK3CA
H1047R - subclonal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of extensive clinical[198-199,428] and preclinical[201] evidence, PIK3CA activation may predict sensitivity to mTOR inhibitors such as temsirolimus. In two studies of temsirolimus-containing treatment regimens in a variety of cancer types, response rates of 4/16 (25%)[198] and 7/23 (30%)[428] were reported in patients with PIK3CA-mutant tumors.

SUPPORTING DATA

A Phase 1, dose-escalation trial combining temsirolimus and radiation/temozolomide therapy, with or without adjuvant temozolomide monotherapy, in patients with newly diagnosed glioblastoma reported no clinical responses but 24/25 patients experienced a period of stable disease; increased infection rates were noted with this regimen[429]. A Phase 1/2 trial of temsirolimus in combination with sorafenib in glioblastoma was terminated at the Phase 2 interim analysis after patients failed to meet the primary endpoint of 6 month progression-free survival; significant toxicity was also observed in the combination therapy, even at low doses of temsirolimus[430]. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit[431]. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma[432]. A Phase 1/2 study of temsirolimus in combination with erlotinib reported 6% (1/16) complete responses, 6% (1/16) partial responses, and 12.5% (2/16) instances of stable disease in patients with anaplastic glioma[433].

Trametinib

Assay findings association

BRAF
V600E - subclonal

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[64-65] , V600K[64], V600R[65], K601E[65,434] , L597V[64], L597Q[434-435] , or L597S[436] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[115]; as well as by patients with tumors harboring BRAF fusions[437-442] .

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[443-444] . A patient with NF1-associated glioblastoma experienced clinical benefit in response to trametinib[445]. A patient with piliocytic astrocytoma harboring an NFIA-RAF1 fusion that had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[446]. 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[384], 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[385].

Vemurafenib

Assay findings association

BRAF
V600E - subclonal

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[54,107,112,447-453] .

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[450,453] . Other studies have reported antitumor activity of vemurafenib for patients with BRAF V600E-mutated PXA[454], glioblastoma[455], or ganglioglioma[456]. Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[54-55,105,107-114,338] . Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[54,75] . In a Phase 1b trial, patients with BRAF V600E-mutant 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[457].

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E - subclonal

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[58-59,458] .

SUPPORTING DATA
The combination of vemurafenib and cobimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[458-460] 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[58-59,461] .

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. | 18 January 2021
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ORDERED TEST # ORD-0991490-01

CLINICAL TRIALS

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
BRAF

RATIONALE
BRAF V600 mutation may predict sensitivity to inhibitors of BRAF, MEK, or ERK.

ALTERATION
V600E - subclonal

NCT03970447

PHASE 2/3

A Trial to Evaluate Multiple Regimens in Newly Diagnosed and Recurrent Glioblastoma

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: Florida, Louisiana, South Carolina, Texas, Mississippi, Georgia, 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
BCL-W, BCL-XL, BCL2, BRAF, MEK

LOCATIONS: Florida, North Carolina, Kansas, Ohio, New Jersey, New York

NCT02857270

PHASE 1

A Study of LY3214996 Administered Alone or in Combination With Other Agents in Participants With Advanced/Metastatic Cancer

TARGETS
ERK1, ERK2, CDK4, CDK6

LOCATIONS: Florida, Texas, Tennessee, District of Columbia, Pennsylvania, Massachusetts, New Hampshire, Villejuif Cedex (France), Sydney (Australia), Nedlands (Australia)

NCT02070549

PHASE 1

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

TARGETS
MEK

LOCATIONS: Florida, Texas, Toronto (Canada)

NCT03973918

PHASE 2

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

TARGETS
BRAF, MEK

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

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

NCT04201457

PHASE 1/2

A Trial of Dabrafenib, Trametinib and Hydroxychloroquine for Patients With Recurrent LGG or HGG With a BRAF Aberration

TARGETS
BRAF, MEK

LOCATIONS: Georgia, Tennessee, District of Columbia, Ohio, Pennsylvania, New York, California

NCT04051606

PHASE 2

Regorafenib in Bevacizumab Refractory Recurrent Glioblastoma

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: Ohio

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

GENE
EGFR

ALTERATION
kinase domain duplication

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Several strategies to overcome resistance are under investigation, including next-generation EGFR TKIs and EGFR inhibitor combinations.

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

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: Texas, Alabama, North Carolina, Tennessee, Oklahoma, Pennsylvania, Toronto (Canada), Arizona

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

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

NCT02638428

PHASE 2

Genomics-Based Target Therapy for Children With Relapsed or Refractory Malignancy

TARGETS
FGFR1, FGFR2, FGFR3, KIT, VEGFRs, ALK, AXL, MET, ROS1, TRKA, TRKC, ABL, DDR2, SRC, FLT3, RAFs, RET, EGFR, mTOR, JAK2, JAK1, ERBB2, BRAF

LOCATIONS: Seoul (Korea, Republic of)

GENE
IDH1

ALTERATION
R132H

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors. Preclinical data indicate that IDH1 mutations may predict sensitivity to glutaminase inhibitors.

NCT03212274

PHASE 2

Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations

TARGETS
PARP

LOCATIONS: Florida, Texas, Georgia, North Carolina, Tennessee, Kentucky, Oklahoma, Maryland, Missouri

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Texas, Tennessee, Massachusetts

NCT03914742

PHASE 1/2

BGB-290 and Temozolomide in Treating Patients With Recurrent Gliomas With IDH1/2 Mutations

TARGETS
PARP

LOCATIONS: Alabama, North Carolina, Virginia, Maryland, Missouri, Pennsylvania, Connecticut, Ohio, Massachusetts, Michigan

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: New York, Massachusetts, California, Saint Herblain (France), Withington (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Villejuif (France), Seoul (Korea, Republic of)

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

NCT04221503

PHASE 2

Niraparib/TTFields in GBM

TARGETS
PARP

LOCATIONS: Pennsylvania

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NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

NCT02813135

PHASE 1/2

European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors

TARGETS
TOP1, CDK6, CDK4, WEE1, PARP, mTORC1, mTORC2, PD-1, KIR, IDH2

LOCATIONS: Villejuif (France), Copenhagen (Denmark)

GENE
PIK3CA

ALTERATION
H1047R - subclonal

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT03893487

PHASE NULL

Fimepinostat in Treating Brain Tumors in Children and Young Adults

TARGETS
HDAC, PI3K

LOCATIONS: Florida, Texas, Tennessee, Maryland, Pennsylvania, Missouri, Ohio, Massachusetts, Michigan, Minnesota

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Florida, Louisiana, Texas

NCT02574728

PHASE 2

Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors

TARGETS
TOP2, mTOR

LOCATIONS: Florida, Georgia, Virginia, Delaware, Missouri, Arizona

NCT03834740

PHASE NULL

Ph0/2 Ribociclib & Everolimus

TARGETS
CDK6, CDK4, mTOR

LOCATIONS: Arizona

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Tennessee, California

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Texas, Massachusetts

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NCT04589845

PHASE 2

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

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

LOCATIONS: Texas, New York, Michigan, Nevada

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, ER, CDK4, CDK6

LOCATIONS: Tennessee, New York, Massachusetts, Toronto (Canada), Valencia (Spain), Bordeaux (France), Barcelona (Spain), Surrey (United Kingdom), London (United Kingdom), Villejuif (France)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York

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.

APC V1125A	***FUBP1*** T561A	***KMT2A (MLL)*** A3440T	***NOTCH1*** R703H
SPEN P748L	***TSC1*** K587R	***VEGFA*** K53E	***ZNF217*** D652H

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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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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. Observed TMB is dependent on characteristics

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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.

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*

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 2.1.0

The median exon coverage for this sample is 370x

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