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 Skin melanoma

DATE OF BIRTH 25 December 1964
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Skin
SPECIMEN ID 2021 Q19170 1A
SPECIMEN TYPE Block
DATE OF COLLECTION 13 May 2021
SPECIMEN RECEIVED 09 June 2021

Biomarker Findings

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

Genomic Findings

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

BRAF V600E
CDKN2A/B p16INK4a V82fs*44 and p14ARF R96fs*71
MLL2 D2769N
TERT promoter -124C>T

2 Disease relevant genes with no reportable alterations: ***KIT, NRAS***

8 Therapies with Clinical Benefit
0 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENOMIC FINDINGS

***BRAF* -** V600E

10 Trials *see p. 14*

ACTIONABILITY

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Dabrafenib + Trametinib	1	Selumetinib
Encorafenib + Binimetinib	1	
Vemurafenib + Cobimetinib	1	
Dabrafenib	2A	
Vemurafenib	2A	
Vemurafenib + Cobimetinib + Atezolizumab	2A	
Trametinib		

NCCN category

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

***MLL2* -** D2769N p. 5

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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.

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

MSI has been detected in 16-32% of cutaneous melanomas in several small datasets, with the majority exhibiting MSI-low[6]. A higher frequency of MSI (low and high) has been reported in metastatic tumors (20-77%) compared to primary tumors (2-30%)[7]. No association between MSI status and clinicopathological features of patients with melanoma was reported in one study[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[9]. 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[9-11]. 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[12-14]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[9,11,13-14].

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[15-17], anti-PD-1 therapies[15-18], and combination nivolumab and ipilimumab[19-24]. In multiple studies of immune checkpoint inhibitors in melanoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-1 or anti-PD-L1 treatments[18,25]. Increased TMB has been associated with longer PFS and OS for patients with melanoma treated with nivolumab, with studies reporting increased benefit for patients with a mutational load above 162 missense mutations per tumor (~equivalency >8 Muts/Mb as measured by this assay)[26]. Increased TMB (~equivalency >10.8 Muts/Mb as measured by this assay) has also been associated with longer PFS and OS for patients with melanoma treated with combination nivolumab and ipilumumab[26]. Improved PFS and OS of patients with melanoma treated with ipilumumab has been observed across all TMB levels[27].

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that various melanoma subtypes harbored median TMBs between 6.3 and 14.4 Muts/Mb, and 25% to 40% of cases had elevated TMBs of greater than 20 Muts/Mb[28]. Malignant melanoma has been reported to have a high prevalence of somatic mutations compared with other tumor types[29], with desmoplastic melanoma ranking among the highest of melanoma subtypes (median TMB of 62 Muts/Mb)[30]. Higher mutational load has been reported in NF1-mutant melanoma samples compared with BRAF-mutant, NRAS-mutant, or BRAF/NRAS/NF1 wild-type samples[25]. In 1 study, elevated TMB correlated with PD-L1 positive status and increased OS in tissue specimens from patients with Stage 3 melanoma[31]. In another study, elevated tissue TMB (>20 Muts/Mb) was associated with longer PFS and OS in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy as compared with patients with lower TMB[25]. Increased TMB has also been associated with histologic stage and cumulative sun exposure[32].

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[33-34] and cigarette smoke in lung cancer[35-36], treatment with temozolomide-based chemotherapy in glioma[37-38], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[39-43], and microsatellite instability (MSI)[39,42-43]. 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[15-16,18,25,44-47].

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GENE
BRAF

ALTERATION
V600E

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

VARIANT ALLELE FREQUENCY (% VAF)
50.9%

POTENTIAL TREATMENT STRATEGIES

BRAF V600 mutations activate MEK-ERK signaling and are associated with sensitivity to BRAF V600 mutation-specific inhibitors such as vemurafenib[48], dabrafenib[49], and encorafenib[50]; the combination of BRAF V600 mutation-selective inhibitors with MEK inhibitors such as encorafenib plus binimetinib[51], vemurafenib plus cobimetinib[52-53], or dabrafenib plus trametinib[54-56]; MEK inhibitors such as trametinib[57-59], cobimetinib[60], binimetinib[61], and selumetinib[62-64]; pan-RAF inhibitors such as sorafenib[65-67]; and ERK inhibitors[68]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs for 16% (3/19) of previously treated patients and 1 out of 2 newly diagnosed patients with BRAF V600E-mutant melanoma, 25% (3/12) of patients with BRAF-mutated lung cancer (2 with V600E and 1 with L597Q), and 19% (4/21) of patients with other BRAF-mutated cancers (2 with G469A, 1 with V600E, and 1 with L485W); 2 patients with BRAF V600E mutations also experienced CNS response[69]. 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[48-49,70]. Meta-analysis confirmed a reduced risk of developing cutaneous SCC with combined BRAF- and MEK-inhibition relative to BRAF-inhibitor monotherapy[71]. A Phase 1/2 trial of PLX8394, a next-generation BRAF inhibitor predicted to not induce paradoxical MAPK pathway activation[72-73], 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)[74]. Although Phase 2 and case studies of sorafenib in BRAF V600-mutated thyroid carcinoma have reported clinical responses[65-66], a patient with a BRAF V600E-mutated NSCLC achieved a PR to sorafenib[67], and a case study has reported that a patient with BRAF-mutated GIST responded to regorafenib treatment[75]. Another patient with BRAF-mutated GIST did not respond to regorafenib treatment[76] and clinical studies in various other diseases have shown conflicting results regarding the correlation between BRAF V600 mutations and efficacy of sorafenib and other pan-RAF inhibitor, such as regorafenib[77-85]; therefore, it is not known whether these agents would be beneficial in this case.

FREQUENCY & PROGNOSIS

BRAF mutations have been reported in 37-66% of melanoma cases[86-89], most frequently in cutaneous melanoma (41-51%)[89-90], melanoma of unknown primary (52%)[91] and conjunctival melanoma (14-29%)[92-93]. There are conflicting reports regarding the prognostic significance of BRAF mutation in the context of melanoma[91,94-96]. In one study of non-acral cutaneous melanoma, BRAF non-V600E mutation associated with some, but not other, clinicopathological features but did not impact OS since Stage 4 diagnosis, including OS after initiation of frontline ipilimumab treatment[97].

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[98-99]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[86,100]. 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[86,89,101]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[86,102]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[48-49,101,103-111]; other mutations at this position are predicted to behave similarly.

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GENE
CDKN2A/B

ALTERATION
p16INK4a V82fs*44 and p14ARF R96fs*71

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
243_244insCGCCACTCTCACCCGACCC

VARIANT ALLELE FREQUENCY (% VAF)
39.8%

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[112-115]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[116-117], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[118-124]; 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[125-126], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS
CDKN2A mutations have been reported in 1-21% of melanoma cases[87-88,127]. Concomitant loss of p16INK4a and p14ARF in melanoma is common, although loss of activity of either may also occur as a result of transcript-specific mutations or hypermethylation[128-134]. Various correlations between CDKN2A alterations and tumor histology or patient prognosis in melanoma have been reported in the literature, with some studies reporting CDKN2A deletion to be associated with adverse prognosis and other studies reporting no association between CDKN2A deletion and prognosis[135-138]. Studies suggest that deletion of CDKN2A is an early event in melanoma tumorigenesis, and loss of p16INK4a has been associated with increased DNA damage in human benign melanocytic tumors and has been suggested to contribute to tumorigenesis by promoting the proliferation of cells with genetic damage[139-140]. CDKN2A alterations affecting p16INK4a, p14ARF, or both have been strongly associated (up to a 76% risk) with familial melanoma[141-151].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[152-153]. 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[154-155]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[156-157]. One or more alterations observed here are predicted to result in p16INK4a loss of function[158-179]. One or more alterations seen here have been observed in the context of cancer but have not been characterized and their effect on p14ARF function is unclear.

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[180]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[181-182]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[183-185]. 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[186-188]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MLL2

ALTERATION
D2769N

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
8305G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.2%

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

FREQUENCY & PROGNOSIS
MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2021)[189], and are especially prevalent in lung squamous cell carcinoma (SCC)[190] and small cell lung carcinoma (SCLC)[191]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[192]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[193]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[194].

FINDING SUMMARY
MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[195]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[196]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[197].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS
Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[198-203]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[202,204-205]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
42.9%

POTENTIAL TREATMENT STRATEGIES

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 22-71% of melanoma cases, including 85% of metastatic melanomas, 66% of unknown primary melanomas, 32% (12/38) of conjunctival melanomas, 13.2% (7/53) of mucosal melanomas, 6% (2/32) of acral lentiginous melanomas, and 1/50 uveal melanomas[206-213]. TERT promoter mutations associate with increased TERT expression in melanoma[208-209,214]. Gains of the TERT locus have also been reported in 31.2% (5/16) of melanomas[215]. TERT promoter mutations or protein overexpression has been associated with poor clinico-pathological features, but not with impact on survival[206-207,214,216]. In addition, germline polymorphisms in TERT have been associated with risk of melanoma development[217-219].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[220]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[221-223]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[208-209,213], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[209].

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Dabrafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[48-49,101,103-110,224] ; 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[48-49,101,103-110,224] . Dabrafenib has shown clinical efficacy for the treatment of melanoma in numerous studies, either as monotherapy[49,101,225-228] or in combination with other targeted therapies[54,56,229-233] . A Phase 3 study of dabrafenib for the treatment of patients with BRAF V600E-mutant metastatic melanoma reported significantly improved median PFS (5.1 vs. 2.7 months, HR=0.30) and ORR (50% vs. 6%, HR=0.61) when compared with dacarbazine[49]. Continual treatment with dabrafenib or vemurafenib past progression on these agents has been shown to further extend survival of patients with melanoma (median post-progression OS, 10.0–11.6 months vs. 2.0–3.4 months)[234-235] . In the Phase 3 COMBI-d and COMBI-v studies, dabrafenib combined with trametinib showed improved median OS (25.1 months and not reached vs. 18.7 and 17.2 months), median PFS (11.0 and 11.4 months vs. 8.8 and 7.3 months), and ORR (68.2% and 64.3% vs. 54.7% and 51.4%) compared with single-agent dabrafenib or vemurafenib, respectively, for treatment-naive patients with BRAF V600E/K-mutated advanced melanoma[54-56] . A pooled analysis reported a 5-year PFS rate of 19% and OS rate of 34% for the combination therapy[236]. In the Phase 3 COMBI-AD trial, adjuvant combination of dabrafenib and trametinib improved median relapse-free survival (RFS; not reached vs. 16.6 months, HR=0.51), the 5-year RFS rate (52% vs. 38%), and the 3-year OS rate (86% vs. 77%, HR=0.57) compared with placebo for patients with resected Stage 3 BRAF V600E/K-mutated melanoma[237-238] . Patients in the Phase 2 COMBI-MB trial with BRAF V600-mutated melanoma and brain metastases achieved a 56.0% intracranial response rate and a 56.8% ORR following treatment with trametinib and dabrafenib[239]. The combination of dabrafenib and trametinib has also been shown to benefit patients with melanoma after delayed progression on vemurafenib or dabrafenib, with an ORR of 14.7% (10/68), median PFS of 3.6 months, and median OS of 10.0 to 11.8 months[232]. The Phase 3 COMBI-i study evaluating dabrafenib and trametinib in combination with spartalizumab reported an ORR of 77.8% (28/36, 15 CRs) in patients with BRAF V600-mutated unresectable or metastatic melanoma, with a median duration of response and median PFS of 20.7 and 23.7 months, respectively, and a 12-month OS rate of 86%[240]. Phase 2 trials have evaluated the triple combination of dabrafenib, trametinib, and either pembrolizumab or nivolumab for first-line treatment of patients with BRAF V600E/K-mutated melanoma; while the addition of pembrolizumab did not result in a statistically significant increase in median PFS (16.0 vs. 10.3 months, HR=0.66, p=0.043)[241], patients with checkpoint inhibitor–resistant tumors receiving the nivolumab combination reported high ORRs (100% in PD-1 inhibitor–naive patients and 83% in PD-1 inhibitor–refractory patients) and improved PFS compared with historical data for dabrafenib plus trametinib (9 vs. 5 months)[242]. A patient with melanoma treated with sequential dabrafenib plus trametinib followed by ipilimumab died due to fatal gastrointestinal toxicity after achieving a CR[233]. 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[49,70,243] . 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[54,56,228,244-245] .

Dabrafenib + Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in various solid tumors and hematologic malignancies, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as dabrafenib and trametinib[54-56,246-251] .

SUPPORTING DATA

In the Phase 3 COMBI-d and COMBI-v studies, dabrafenib combined with trametinib (DT) showed improved median OS (mOS; 25.1 months and not reached vs. 18.7 and 17.2 months), median PFS (mPFS; 11.0 and 11.4 months vs. 8.8 and 7.3 months), and ORR (68.2% and 64.3% vs. 54.7% and 51.4%) compared with single-agent dabrafenib or vemurafenib, respectively, for treatment-naive patients with BRAF V600E/K-mutated advanced melanoma[54-56] . A pooled analysis reported a 5-year PFS rate of 19% and OS rate of 34% for the combination therapy[236]. In the Phase 3 COMBI-AD trial, 12 months of adjuvant DT treatment improved the 5-year relapse-free survival (RFS) (52% vs. 36%) and the 3-year OS (86% vs. 77%, HR=0.57) rates as compared with placebo for patients with resected Stage 3 BRAF V600E/K-mutated melanoma[237,252] . Phase 2 trials evaluating neoadjuvant DT for patients with BRAF V600E/K-mutated melanoma reported ORRs of 85% and 86% (n=13 and 35, respectively), median RFS of 23.3 months (n=35), and significantly longer median event-free survival than standard of care (19.7 months vs. 2.9 months; n=14 and 7, respectively)[253-254] . Patients in the Phase 2 COMBI-MB trial with BRAF V600-mutated melanoma and brain metastases achieved a 56% intracranial response rate and a 56.8% ORR following DT treatment[239]. A Phase 2 trial reported a 32% ORR (n=25) for patients with BRAF V600-mutated melanoma who had progressed on a prior BRAF inhibitor and were rechallenged with DT, including 6 PRs for patients with prior DT treatment[255]. DT has also been shown to benefit patients with melanoma after delayed progression on vemurafenib or dabrafenib, with an ORR of 14.7% (10/68), mPFS of 3.6 months, and mOS of 10.0 to 11.8 months[232]. The Phase 3 COMBI-i study evaluating DT in combination with spartalizumab reported an ORR of 77.8% (28/36, 15 CRs) for patients with BRAF V600-mutated unresectable or metastatic melanoma, with a median duration of response and mPFS of 20.7 and 23.7 months, respectively, and a 12-month OS rate of 86%[240]. Phase 2 trials have evaluated the triple combination of DT and either pembrolizumab or nivolumab for first-line treatment of patients with BRAF V600E/K-mutated melanoma; while the addition of pembrolizumab did not result in a statistically significant increase in mPFS (16.0 vs. 10.3 months, HR=0.66, p=0.043)[241], patients with checkpoint inhibitor-resistant tumors receiving the nivolumab combination reported high ORRs (100% in PD-1 inhibitor-naive patients and 83% in PD-1 inhibitor-refractory patients) and improved PFS compared with historical data for dabrafenib plus trametinib (9 vs. 5 months)[242]. A patient with melanoma treated with sequential dabrafenib plus trametinib followed by ipilimumab died due to fatal gastrointestinal toxicity after achieving a CR[233]. Patients with BRAF V600-mutated melanoma and prior treatment with PD-1 therapy achieved median OS of 15.6 months when treated with a BRAF/MEK inhibitor combination[256].

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical efficacy in the treatment of patients with BRAF V600-mutated melanoma[51,257-259], and activity in colorectal, thyroid, and lung cancer[259-261], activating alterations affecting BRAF predict sensitivity to the combination of encorafenib and binimetinib.

SUPPORTING DATA

In the Phase 3 COLUMBUS trial, the combination of encorafenib and binimetinib exhibited enhanced efficacy as compared with vemurafenib or encorafenib monotherapy for patients with BRAF V600-mutant melanoma (ORR of 63.5% [122/192] vs. 40.8% [78/191] vs. 51.5% [100/194]; median PFS [mPFS] of 14.9 vs. 7.3 vs. 9.6 months; median OS [mOS] of 33.6 vs. 16.9 vs. 23.5 months)[51,257]. Responses in the COLUMBUS trial were durable, with a 4-year OS rate of 39% for the combination and 37% and 26% for encorafenib and vemurafenib monotherapies, respectively[262]. In the Phase 2 LOGIC2 study, encorafenib plus binimetinib elicited ORRs of 73.3% (n=75; 9 CRs, 46 PRs) for BRAF-inhibitor-naive patients and 24.1% (n=83; 3 CRs, 17 PRs) for patients who were previously treated; for patients who progressed on this combination, limited benefit was observed with subsequent addition of ribociclib (n=38; 1 PR, 26.3% DCR), buparlisib (n=6; 16.7% DCR), capmatinib (n=13; 15.4% DCR), or infigratinib (n=1; 0% DCR)[263]. In a Phase 2 trial for BRAF-inhibitor-naive patients with V600-mutant melanoma, the combination of binimetinib, encorafenib, and the CDK4/6 inhibitor ribociclib elicited an ORR of 52.4% (n=42; 5 CRs, 17 PRs), mPFS of 9.2 months, and mOS of 19.4 months[264]. Intracranial responses were observed in a retrospective case series of 24 (3 CRs, 5 PRs) patients with Stage 4 melanoma and BRAF mutation treated with encorafenib and binimetinib, including for all 3 inhibitor-naive patients[258]. Patients with BRAF V600-mutated melanoma and prior treatment with PD-1 therapy achieved median OS of 15.6 months when treated with a BRAF/MEK inhibitor combination[256]. 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[264].

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Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activating BRAF alterations may predict sensitivity to MEK inhibitors such as trametinib. Significant clinical responses to trametinib have been achieved by patients with melanoma harboring BRAF V600E[58-59] , V600K[58], V600R[59], K601E[59,265] , L597V[58], L597Q[265-266] , or L597S[267] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[111]; as well as by patients with tumors harboring BRAF fusions[268-273] .

SUPPORTING DATA

Trametinib in combination with other targeted therapies has shown clinical efficacy for the treatment of melanoma in the context of BRAF V600 mutations[54-55,232-233,236-237,241-242] . In the Phase 3 COMBI-d and COMBI-v studies, dabrafenib combined with trametinib showed improved median OS (25.1 months and not reached vs. 18.7 and 17.2 months), median PFS (11.0 and 11.4 months vs. 8.8 and 7.3 months), and ORR (68.2% and 64.3% vs. 54.7% and 51.4%) compared with single-agent dabrafenib or vemurafenib, respectively, for treatment-naive patients with BRAF V600E/K-mutated advanced melanoma[54-56] . A pooled analysis reported a 5-year PFS rate of 19% and OS rate of 34% for the combination therapy[236]. In the Phase 3 COMBI-AD trial, adjuvant combination of dabrafenib and trametinib improved median relapse-free survival (RFS; not reached vs. 16.6 months, HR=0.51), the 5-year RFS rate (52% vs. 38%), and the 3-year OS rate (86% vs. 77%, HR=0.57) compared with placebo for patients with resected Stage 3 BRAF V600E/K-mutated melanoma[237-238] . Patients in the Phase 2 COMBI-MB trial with BRAF V600-mutated melanoma and brain metastases achieved a 56.0% intracranial response rate and a 56.8% ORR following treatment with trametinib and dabrafenib[239]. The combination of dabrafenib and trametinib has also been shown to benefit patients with melanoma after delayed progression on vemurafenib or dabrafenib, with an ORR of 14.7% (10/68), median PFS of 3.6 months, and median OS of 10.0 to 11.8 months[232]. The Phase 3 COMBI-i study evaluating dabrafenib and trametinib in combination with spartalizumab reported an ORR of 77.8% (28/36, 15 CRs) in patients with BRAF V600-mutated unresectable or metastatic melanoma, with a median duration of response and median PFS of 20.7 and 23.7 months, respectively, and a 12-month OS rate of 86%[240]. Phase 2 trials have evaluated the triple combination of dabrafenib, trametinib, and either pembrolizumab or nivolumab for first-line treatment of patients with BRAF V600E/K-mutated melanoma; while the addition of pembrolizumab did not result in a statistically significant increase in median PFS (16.0 vs. 10.3 months, HR=0.66, p=0.043)[241], patients with checkpoint inhibitor–resistant tumors receiving the nivolumab combination reported high ORRs (100% in PD-1 inhibitor–naive patients and 83% in PD-1 inhibitor–refractory patients) and improved PFS compared with historical data for dabrafenib plus trametinib (9 vs. 5 months)[242]. A patient with melanoma treated with sequential dabrafenib plus trametinib followed by ipilimumab died due to fatal gastrointestinal toxicity after achieving a CR[233]. 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[274], 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[275].

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Vemurafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of strong clinical data, BRAF V600E mutations may confer sensitivity to V600-targeted therapies such as vemurafenib[48,103,108,276-282] .

SUPPORTING DATA

One study reported near-CR to vemurafenib in a patient with BRAF V600K-mutant melanoma who subsequently developed chronic myelomonocytic leukemia (CMML) with NRAS G12R mutation, and concurrent cobimetinib treatment led to suppression of CMML[283]. In a Phase 3 trial vemurafenib improved median OS (HR=0.70) and PFS (HR=0.38) compared to dacarbazine in patients with treatment-naïve metastatic BRAF V600E- or V600K-mutant melanoma[48]. A Phase 3 study for patients with metastatic BRAF V600E/K-mutated melanoma who were previously treated with trametinib reported vemurafenib monotherapy elicited further improvement in median PFS (5.2 months) and OS (8.3 months)(Gogas et al., 2014 ASCO Abstract 9061). The Phase 3 BRIM8 trial comparing vemurafenib to placebo found improved disease-free survival (DFS) for patients with earlier-stage melanoma (not reached vs. 36.9 months), whereas the primary endpoint of DFS was not met for patients with advanced (Stage IIIC) melanoma[284]. Case reports have also documented responses to vemurafenib in patients with metastatic melanoma harboring a BRAF V600R mutation[101], including responses in brain metastases[106-107] . The Phase 3 coBRIM study of 495 patients with V600 mutation-positive melanoma treated either with vemurafenib plus cobimetinib or with vemurafenib and placebo (control group) reported improved median PFS (12.3 vs. 7.2 months, HR=0.58) and median OS (22.3 vs. 17.4 months, HR=0.70) in the combination group; benefit of cobimetinib was observed regardless of prognostic factors, and disease progression did not correlate with concurrent alterations in the RAS pathway[52,285] . Extended 5-year survival analysis from the Phase 1b BRIM7 study of cobimetinib combined with vemurafenib for patients with BRAF V600-mutated melanoma reported a median OS of 31.8 months for BRAF inhibitor-naive patients and 8.5 months for patients who had disease progression on vemurafenib monotherapy[53]. The Phase 3 IMspire150 study of the triple combination of vemurafenib, cobimetinib, and atezolizumab for patients with unresectable Stage IIIc-IV BRAF V600-mutated melanoma showed improved median PFS (16.1 vs. 12.3 months, HR 0.85, as assessed by the independent review committee) compared with the combination of vemurafenib and cobimetinib[286]. 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[48,70] . 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[287].

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in melanoma and colorectal carcinoma, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as vemurafenib and cobimetinib[52-53,288] .

SUPPORTING DATA

Patients with BRAF V600-mutated melanoma and prior treatment with PD-1 therapy achieved median OS of 15.6 months when treated with a BRAF/MEK inhibitor combination[256]. The Phase 3 coBRIM study of 495 patients with V600 mutation-positive melanoma treated either with vemurafenib plus cobimetinib or with vemurafenib and placebo (control group) reported improved median PFS (12.3 vs. 7.2 months, HR=0.58) and median OS (22.3 vs. 17.4 months, HR=0.70) in the combination group; benefit of cobimetinib was observed regardless of prognostic factors, and disease progression did not correlate with concurrent alterations in the RAS pathway[52,285] . Extended 5-year survival analysis from the Phase 1b BRIM7 study of cobimetinib combined with vemurafenib for patients with BRAF V600-mutated melanoma reported a median OS of 31.8 months for BRAF inhibitor-naive patients and 8.5 months for patients who had disease progression on vemurafenib monotherapy[53]. The Phase 3 IMspire150 study of the triple combination of vemurafenib, cobimetinib, and atezolizumab for patients with unresectable Stage IIIc-IV BRAF V600-mutated melanoma showed improved median PFS (16.1 vs. 12.3 months, HR 0.85, as assessed by the independent review committee) compared with the combination of vemurafenib and cobimetinib[286].

Vemurafenib + Cobimetinib + Atezolizumab

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations, cobimetinib is a MEK inhibitor, and atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. The combination is FDA approved to treat patients with melanoma with BRAF V600 mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma and anaplastic thyroid carcinoma, BRAF V600 mutations may confer sensitivity to the combination of vemurafenib, cobimetinib, and atezolizumab[286,289-290] .

SUPPORTING DATA

The Phase 3 IMspire150 study of the triple combination of vemurafenib, cobimetinib, and atezolizumab for patients with unresectable Stage IIIc-IV BRAF V600-mutated melanoma showed improved median PFS (16.1 vs. 12.3 months, HR 0.85, as assessed by the independent review committee) compared with the combination of vemurafenib and cobimetinib[286].

Selumetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence demonstrating the efficacy of selumetinib in patients with BRAF V600-mutated papillary thyroid cancer[291], melanoma,[64,292-295] and low grade glioma[63], as well as in patients with BRAF fusion-positive glioma[62-63] , BRAF activating alterations may predict sensitivity to selumetinib.

SUPPORTING DATA

In the DOC-MEK Phase 2 trial in BRAF wild type advanced melanoma, addition of selumetinib to docetaxel did not result in a significant difference in median PFS (4.23 months) compared to docetaxel plus placebo (3.93 months)[296], and NRAS mutation was associated with inferior OS, and not with PFS[296]. Although unconfirmed responses were higher with selumetinib (32%) than placebo (14%), the difference was not significant (p = 0.059), and selumetinib was associated with lower OS (9.5 months vs 11.4 months) and was less well tolerated than placebo[296]. In a Phase 2 trial of first line treatment of BRAF-mutant metastatic melanoma, addition of selumetinib to dacarbazine resulted in increased PFS compared to dacarbazine plus placebo (5.6 months versus 3.0 months although overall survival did not differ significantly (median 13.9 months for selumetinib compared to 10.5 months for placebo, HR 0.93, p=0.39)[64]. A Phase 2 trial of selumetinib monotherapy versus temozolomide in advanced melanoma unselected for BRAF/NRAS mutation reported no significant differences in PFS (HR = 1.07) or ORR, although PR to selumetinib was more frequently observed in those with BRAF mutations[292]. A durable CR of 4 years has been reported in 1 patient with BRAF-mutated Stage 4 melanoma treated with selumetinib monotherapy[294-295] .

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

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
BRAF

ALTERATION
V600E

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK.

NCT03543969

PHASE NULL

Adaptive BRAF-MEK Inhibitor Therapy for Advanced BRAF Mutant Melanoma

TARGETS
MEK, BRAF

LOCATIONS: Florida

NCT02224781

PHASE 3

Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma

TARGETS
PD-1, CTLA-4, BRAF, MEK

LOCATIONS: Florida, Georgia, Louisiana, South Carolina

NCT03911869

PHASE 2

An Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-mutant Melanoma Brain Metastasis

TARGETS
BRAF, MEK

LOCATIONS: Rosario (Argentina), Buenos Aires (Argentina), Texas, New Jersey, Edegem (Belgium), Colorado, California, Oregon

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, Texas, North Carolina, Kansas

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

NCT02428712

PHASE 1/2

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

TARGETS
BRAF, CRAF

LOCATIONS: Florida, Texas, New York, Arizona

NCT03554083

PHASE 2

Neoadjuvant Combination Targeted and Immunotherapy for Patients With High-Risk Stage III Melanoma

TARGETS
MEK, PD-L1, BRAF

LOCATIONS: Florida, Minnesota

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)

NCT03898908

PHASE 2

Encorafenib and Binimetinib Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain

TARGETS
BRAF, MEK

LOCATIONS: Las Palmas de Gran Canaria (Spain), Sevilla (Spain), Málaga (Spain), Lugo (Spain), Córdoba (Spain), Madrid (Spain), Santander (Spain), El Palmar (Spain), Valencia (Spain), Pamplona (Spain)

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.

BRCA1	*BRCA2*	*IRS2*	*PRDM1*
E1250K	K285N	M498L	K188E

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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

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 4.1.0

The median exon coverage for this sample is 957x

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