FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

COUNTRY CODE
PE

REPORT DATE
08 Feb 2021

ORDERED TEST #
ORD-0998537-01

ABOUT THE TEST FoundationOne® Heme is a comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas.

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)

DATE OF BIRTH 11 September 1936
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Rebagliati
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 320968
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID H21-00341 (Q20-19864)
SPECIMEN TYPE Block
DATE OF COLLECTION 23 December 2020
SPECIMEN RECEIVED 20 January 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

ALK **EML4-ALK fusion (Variant 2)**

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

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 2 Muts/Mb

GENOMIC FINDINGS

ALK **-** EML4-ALK fusion (Variant 2)

10 Trials *see p. 7*

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)
Alectinib	1	none
Brigatinib	1	
Ceritinib	1	
Crizotinib	1	
Lorlatinib	1	
Entrectinib		

☐ *NCCN category*

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

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.

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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-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

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]. 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[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
2 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[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-30]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,31-38]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[39], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[40], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[41]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[42]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[43-44], several other large studies did find a strong association with increased TMB[45-48]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[49]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[43]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[50]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[50-51].

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[52-53] and cigarette smoke in lung cancer[31,54], treatment with temozolomide-based chemotherapy in glioma[55-56], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[57-61], and microsatellite instability (MSI)[57,60-61]. 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[22-23,26-28,31-38,62].

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GENE
ALK

ALTERATION
EML4-ALK fusion (Variant 2)

POTENTIAL TREATMENT STRATEGIES

ALK mutations or rearrangements may confer sensitivity to ALK TKIs such as crizotinib[63-64], ceritinib[65], brigatinib[66-67], alectinib[68], lorlatinib[69], and entrectinib[70]. An ongoing Phase 2 study of lorlatinib for patients with ALK- positive NSCLC previously treated with second-generation TKIs reported an intracranial ORR of 54% and an extracranial ORR of 37%[71]. Lorlatinib also elicited significant clinical activity for patients with NSCLC and intracranial[72] or intrathecal[73] metastases and against resistance mutations associated with progression on first- and second-generation ALK TKIs such as G1202R[74-75]. Crizotinib[76], ceritinib[77], and lorlatinib[78-79] further displayed antitumor activity against ALK+ inflammatory myofibroblastic tumors (IMTs) in Phase 1/2 trials. Phase 1 studies of the ALK/ROS1/TRK inhibitor entrectinib have reported responses for 4 of 7 (57%) kinase inhibitor-naive patients with ALK-rearranged solid tumors, including patients with NSCLC, renal cell carcinoma, and colorectal cancer, but in 0 of 13 patients with ALK fusion-positive tumors previously treated with an ALK inhibitor and in none of the other patients with ALK non-fusion alterations[70]. A Phase 1/1B trial of entrectinib for children and adolescents with recurrent or refractory solid tumors reported responses in patients with infantile fibrosarcoma (IFS; 1 CR) or inflammatory myofibroblastic tumor (IMT; 1PR) harboring ALK fusions[80]. A Phase 2 trial of the HSP90 inhibitor ganetespib reported PRs for a small number of patients with ALK-rearranged NSCLC[81]. A Phase 3 study for patients with inhibitor-naive ALK-positive non-small cell lung cancer (NSCLC) reported superior clinical benefit with ensartinib, a second-generation ALK inhibitor, compared with crizotinib treatment (median PFS 25.8 vs. 12.7 months [HR=0.51], ORR 75% vs. 67%, 36-month duration of response [DOR] 59% vs. 27%); intracranial activity of ensartinib for these patients was also improved compared with crizotinib (ORR 64% [7/11] vs. 21% [4/19])[82]. A Phase 2 study for patients with ALK-positive NSCLC who progressed on crizotinib reported an overall ORR of 52%, a median PFS of 9.6 months, and an intracranial ORR of 70% (28/40)[83]. The Phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC[84]; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

ALK rearrangements are frequently observed in lung adenocarcinomas[85-87]. The EML4-ALK gene fusion has been observed in approximately 3-7% of non-small cell lung carcinoma cases, more frequently in younger patients, non-smokers, females, and patients of Asian heritage[88-94]. ALK protein expression has been associated with poor prognosis in some cancer types, including NSCLC, renal cell carcinoma, and neuroblastoma[95-97]. EML4-ALK fusions have been reported to be a significant indicator of poor prognosis in advanced stage NSCLC[94].

FINDING SUMMARY

ALK encodes a receptor tyrosine kinase, a member of the insulin receptor superfamily, whose activation induces the downstream pathways associated with cell survival, angiogenesis, and cell proliferation[98]. Different EML4-ALK variants have been identified in cancer, all of which contain the intracellular tyrosine kinase domain of ALK[99]. The most commonly observed rearrangements consist of ALK exon 20 fused to a variety of breakpoints in EML4: exon 13 (variant 1, 33-54% of cases)[100-103], exon 20 (variant 2, 10-12% of cases)[100-103], exon 6 (variant 3 a/b, 26-44% of cases)[100-101,103-105], exon 15 (variant 4, 2% of cases)[89,106-107], exon 18 (variant 5, 1.6-3% of cases)[102,106], exon 2 (variant 5 a/b, 1-2% of cases)[100,107-109], and exon 17 (variant 8 a/b, less than 1%)[102,106,110]. All of these variants have been characterized as, or are predicted to be, activating and sensitive to ALK inhibitors, including crizotinib and ceritinib[101,104,111]; however, variants 3a/b are less sensitive to crizotinib in vitro[101,103]. Although retrospective analyses of crizotinib-treated non-small cell lung cancer (NSCLC) have reported significant differences in outcomes among EML4-ALK variants, specifically longer median progression-free survival (PFS) in patients with variant 1 and improved 2-year PFS and time to progression in patients with variants other than 3a/b[103,112-113], other studies have not found correlation between EML4-ALK variants and response to crizotinib in NSCLC[102,105].

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Alectinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET and is FDA approved to treat patients with ALK-positive, metastatic non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating ALK alterations may predict sensitivity to alectinib on the basis of extensive clinical evidence in ALK-rearranged NSCLC[114-118] .

SUPPORTING DATA

Alectinib has been primarily studied for the treatment of ALK-rearranged NSCLC. In the Phase 3 ALEX study comparing alectinib with crizotinib in ALK-rearranged, inhibitor-naive NSCLC, patients treated with alectinib experienced significantly improved median PFS (34.8 vs. 10.9 months; HR=0.43), with PFS benefit observed in patients with EML4-ALK variants 1, 2, and 3a/b[68,119] . Similar results have been reported in the J-ALEX trial for inhibitor-naive Japanese patients with ALK-positive NSCLC[120-121] . For patients with crizotinib-refractory ALK-rearranged NSCLC, Phase 1/2 and Phase 2 trials of alectinib reported ORRs of 45% to 55%[117-118,122] , and the Phase 3 ALUR trial showed that alectinib significantly improved PFS compared with chemotherapy (7.1 vs. 1.6 months; HR=0.32)[123]. Alectinib has demonstrated significant activity against central nervous system (CNS) metastases for patients with NSCLC, with improved CNS-specific ORRs compared with chemotherapy (54.2% [13/24] vs. 0% [0/16])[123] or crizotinib (81% [17/21] vs. 50% [11/22])[68,116-118,122,124-130] . Alectinib combined with atezolizumab led to an ORR of 81% (17/21) as first-line treatment for PD-L1 unselected, ALK+ NSCLC[131].

Brigatinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Brigatinib is a kinase inhibitor that targets ALK, ROS1, and mutant EGFR and is FDA approved to treat patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating ALK alterations may predict sensitivity to brigatinib based on strong clinical[66,132-133] and preclinical[134-135] evidence.

SUPPORTING DATA

Brigatinib has been studied primarily for the treatment of ALK-rearranged NSCLC[133,136-137] . Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations[66]. An initial Phase 1/2 study of brigatinib for the treatment of patients with ALK-rearranged NSCLC reported responses in 71.8% (51/71) of crizotinib-pretreated patients and in 100.0% (8/8) of crizotinib-naive patients with median PFSs of 13.2 months and unreached, respectively (Gettinger et al., 2016;). Interim analyses of the Phase 3 ALTA-1L study comparing brigatinib to crizotinib for front-line treatment of patients with ALK-positive NSCLC show a superior median PFS (24.0 vs. 11.0 months, HR=0.49) and a significantly higher intracranial ORR (78% vs. 30%) with brigatinib[137-138] . The Phase 2 ALTA study demonstrated the activity of brigatinib with 2 different dosing regimens following progression on crizotinib for patients with ALK-positive NSCLC, reporting ORRs of 46% and 56%, median PFSs of 9.2 and 16.7 months, and median OSs of 29.5 and 34.1 months[139]. The intracranial activity of brigatinib has been demonstrated in multiple studies[67,139] with the ALTA study reporting intracranial ORRs of 50.0% (13/26) and 66.7% (12/18), median duration of intracranial responses of 9.4 and 16.6 months, and median intracranial PFSs of 12.8 and 18.4 months[139]. A retrospective study reported an ORR of 16.7% (3/18), a DCR of 66.7% (12/18), and a median PFS of 4.4 months for patients with ALK-positive alectinib-refractory NSCLC treated with brigatinib[140].

Ceritinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is FDA approved to treat metastatic non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements, as detected by an FDA-approved test. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data demonstrating benefit to patients with NSCLC[65,141-146] , inflammatory myofibroblastic tumors, and anaplastic large cell lymphoma[147], ALK rearrangements may predict sensitivity to ceritinib. In ALK-rearranged NSCLC, responses to ceritinib have been observed in crizotinib-naïve patients[65,141,144] as well as after relapse on crizotinib[65,142-143,145-146] .

SUPPORTING DATA

Ceritinib has been shown to confer clinical benefit in patients with ALK/ROS1-rearranged NSCLC[144,148] . Multiple Phase 3 studies have reported clinical benefit from ceritinib for patients with advanced ALK-rearranged (ALK+) NSCLC. As a first-line treatment for patients with ALK+ NSCLC in the ASCEND-4 Phase 3 study, ceritinib monotherapy significantly increased the median PFS to 16.6 months, compared to a median PFS of 8.1 months in patients with platinum-based chemotherapy[144]. A Phase 3 study of ceritinib for ALK inhibitor naive patients with ALK+ NSCLC observed a whole-body (WB) ORR of 63.7%, a WB DCR of 89.5%, and PFS of 11.1 months[141]. The ASCEND-5 Phase 3 study comparing ceritinib to chemotherapy for patients with ALK+ NSCLC previously treated with crizotinib and chemotherapy also reported a significant benefit from ceritinib in ORR (39% vs. 7%) and median PFS (5.4 vs. 1.6 months); there was no improvement of median OS (18.1 vs. 20.1 months), which may be due to the crossover of patients to the ceritinib arm[143]. The ASCEND-1 Phase 1 study of ceritinib for patients with ALK+ NSCLC reported an ORR of 72%, median PFS of 18.4 months, and 12-month OS of 83%[65]. Earlier Phase 1 and 2 studies reported similar clinical benefit as measured by ORR (39-57%), median PFS (5.7-6.9 months), and median OS of 16.7 months[65,145-146] ; for patients with brain metastases, an intracranial ORR of 39% and duration of response of 12.8 months were achieved[142]. In patients with ALK/ROS1-rearranged NSCLC, ceritinib treatment resulted in confirmed PRs in 73% (19/26) with a DCR of 92%[149]. Case studies have also reported responses to ceritinib in patients with ALK+ NSCLC and ALK missense mutation after disease progression on crizotinib[150] or alectinib[151-152] .

Crizotinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), and to treat pediatric and young adult patients with ALK rearrangement-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

ALK activation may predict sensitivity to crizotinib. In patients with ALK-rearranged non-small cell lung cancer (NSCLC), crizotinib improved outcomes in both the first-line[64,153] and second-line[154] settings compared with chemotherapy. ALK inhibitors have also demonstrated clinical activity in the context of several other cancer types with activating ALK alterations, including thyroid carcinoma, colorectal carcinoma, inflammatory myofibroblastic tumor, and anaplastic large cell lymphoma[155-160] .

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[64,112,153-154,161] , ROS1 rearrangements[162-166] , an NTRK1 fusion[167], or MET activation[168-184] . Three Phase 3 studies for patients with ALK-positive NSCLC reported superior PFS (7.7-11.1 vs. 3.0-7.0 months) and ORR (65.0%-87.5% vs. 20.0%-45.6%) when treated with crizotinib compared with chemotherapy regimens in various settings[64,153,161] . The efficacy of crizotinib for patients with brain metastases has also been examined. Prospective comparison of the intracranial efficacy for patients with stable, treated brain metastases included in the PROFILE 1014 study reported significantly prolonged intracranial disease control rate (DCR) at 24 weeks (56% vs. 25%) and PFS (9.0 vs. 4.0 months, HR= 0.40) for patients treated with first-line crizotinib as compared with chemotherapy[185]. A pooled retrospective analysis of patients with ALK-rearranged NSCLC and concurrent brain metastases from the PROFILE 1007 and 1005 studies reported 12-week intracranial DCRs of 56% versus 62% and intracranial ORRs of 18% versus 33% for patients with previously untreated versus previously treated brain metastases[186]. In a retrospective study of 90 patients with brain metastases from ALK-rearranged NSCLC, the median OS after diagnosis of brain metastasis was 49.5 months; lack of prior targeted therapy, absence of extracranial metastasis, and a Karnofsky performance score of 90 or higher were significantly associated with improved OS[187]. Upon disease progression, further survival benefit has been observed for patients with ALK-positive NSCLC who continue crizotinib treatment[188].

Entrectinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is FDA approved to treat adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients with NTRK fusion-positive solid tumors that lack a known acquired resistance mutation and are metastatic or likely to result in severe morbidity after surgical resection, have no satisfactory alternative treatments, or have progressed following treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in NSCLC, neuroblastoma, and other solid tumors[70,80,189-190] , ALK fusions or activating mutations may predict sensitivity to entrectinib.

SUPPORTING DATA

A Phase 1 trial of entrectinib reported PRs for 2/4 patients with ALK-rearranged NSCLC, with 1 patient experiencing ongoing clinical benefit for more than 2 years[70]. Phase 1 trials have reported a combined 66.7% ORR (1 CR, 5 PRs; n=9) for patients with ALK-rearranged solid tumors treated with entrectinib; responses were observed for patients with NSCLC (2/4), renal cell carcinoma (1/1), colorectal cancer ([CRC], 1/1), and inflammatory myofibroblastic tumors (2/2), but not for a patient with an unknown primary tumor[70,191] . Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without CNS metastases and with NTRK, ROS1, or ALK fusions[70,80,192-195] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[196]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutant neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received prior ALK TKI or crizotinib, respectively[70].

Lorlatinib

Assay findings association

ALK
EML4-ALK fusion (Variant 2)

AREAS OF THERAPEUTIC USE

Lorlatinib is a tyrosine kinase inhibitor that targets ALK and ROS1. It is FDA approved to treat patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) following disease progression on crizotinib, alectinib, or ceritinib. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in NSCLC[197-198] , case studies in inflammatory myofibroblastic sarcoma[78-79] , and preclinical evidence in multiple cell types[74,199-202] , ALK activation may predict sensitivity to lorlatinib.

SUPPORTING DATA

Lorlatinib has primarily been investigated for ALK- and ROS1-positive NSCLC as an approach to overcome resistance to prior TKIs[69,203] . In the Phase 3 CROWN study for the first-line treatment of ALK-positive non-small cell lung cancer (NSCLC), lorlatinib was shown to be superior to crizotinib, with significantly improved median PFS (mPFS; not estimable vs. 9.3 months, HR=0.28) and higher overall ORR (76% vs. 58%) and intracranial ORR (82.4% [14/17] vs. 23.1% [3/13])[198]. In a pivotal Phase 2 study for patients with ALK-positive NSCLC who had progressed on one or more ALK TKIs, lorlatinib elicited a 47% ORR, a 63.0% (51/81) intracranial ORR, and mPFS of 7.3 months[197]; the ORR was 40% for patients previously treated with 1 or more second-generation TKIs[204]. In this study, lorlatinib reduced the incidence of first intracranial progression for patients with prior central nervous system metastases[203]. For patients whose tumors harbored 1 or more ALK kinase domain mutations, lorlatinib led to responses for 64.4% (29/45), including 57.1% (16/28) of those with the ALK G1202R resistance mutation[205]; G1202, therefore, does not appear to represent a major mechanism of lorlatinib resistance[74-75,206] . In an expansion cohort of a Phase 1/2 study, patients with ALK-positive NSCLC who remained on lorlatinib following progression exhibited improved OS and OS post-PD relative to patients who received another treatment or no subsequent treatment[207]. In the JAVELIN Lung 101 study, the combination of lorlatinib and avelumab led to an ORR of 46.4% (13/28) for patients with ALK-positive NSCLC[208].

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.

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
ALK

ALTERATION
EML4-ALK fusion (Variant 2)

RATIONALE
ALK rearrangements, activating mutations, or amplification may predict sensitivity to ALK inhibitors as well as HSP90 inhibitors.

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: Washington, Oregon, California, Utah, North Dakota, Arizona, South Dakota, Nebraska

NCT02201992

PHASE 3

Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial)

TARGETS
ALK, AXL, MET, ROS1, TRKA, TRKC

LOCATIONS: Washington

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Washington, Edmonton (Canada), California, Colorado, Minnesota

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Washington, Utah, Nevada, California, Colorado, Arizona

NCT03737994

PHASE 2

Biomarker/ALK Inhibitor Combinations in Treating Patients With Stage IV ALK Positive Non-Small Cell Lung Cancer (The NCI-NRG ALK Master Protocol)

TARGETS
ALK, RET, EGFR, ROS1, ABL, AXL, MET, TRKA, TRKC

LOCATIONS: Washington, Idaho

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NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), London (Canada), Toronto (Canada), Kingston (Canada), Ottawa (Canada), Montreal (Canada)

NCT03596866

PHASE 3

An Efficacy Study Comparing Brigatinib Versus Alectinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer Participants Who Have Progressed on Crizotinib

TARGETS
ALK, EGFR, ROS1, RET

LOCATIONS: California, Toronto (Canada), Aguascalientes (Mexico), Georgia, Virginia, Ciudad de Mexico (Mexico), New York, Halifax (Canada), Uppsala (Sweden), Solna (Sweden)

NCT03087448

PHASE 1/2

Ceritinib + Trametinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

TARGETS
MEK, ROS1, ALK

LOCATIONS: California

NCT04005144

PHASE 1

Brigatinib and Binimetinib in Treating Patients With Stage IIIB-IV ALK or ROS1-Rearranged Non-small Cell Lung Cancer

TARGETS
MEK, ALK, EGFR, ROS1

LOCATIONS: California

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: California, Tennessee, Connecticut

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
S2421L

CREBBP
V2048M

FANCD2
R328Q

KMT2C (MLL3)
A846V

MLL2
Q3919_L3920insQ

NF1
L484P

PCLO
I1122M

SETD2
S379R

STAT6
rearrangement

TRAF2
L422V and T226M

TSC1
K587R

WDR90
E351D

ZNF217
P803S

Electronically signed by Richard Huang, M.D. | 08 February 2021
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FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*	*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*
B2M	*BAP1*	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*
BCL7A	*BCOR*	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*
BRD4	*BRIP1*	*BRSK1*	*BTG2*	*BTK*	*BTLA*	*C11orf30 (EMSY)*	*CAD*
*CALR**	*CARD11*	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*
CCT6B	*CD22*	*CD274 (PD-L1)*	*CD36*	*CD58*	*CD70*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1B*	*CDKN2A*
CDKN2B	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*	*CIITA*
CKS1B	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*
EGFR	*ELP2*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*
ERBB3	*ERBB4*	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*
FAF1	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*	*FANCG*
FANCL	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FHIT	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*	*FOXO1*
FOXO3	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4 (C17orf39)*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*
GTSE1	*HDAC1*	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*
HIST1H2AC	*HIST1H2AG*	*HIST1H2AL*	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*
HIST1H3B	*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*	*IDH1*	*IDH2*
IGF1R	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*	*INPP4B*
INPP5D (SHIP)	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*
KDR	*KEAP1*	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*
LEF1	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*
MDM2	*MDM4*	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*
MITF	*MKI67*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*
MTOR	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*
NCSTN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*	*NOTCH1*
NOTCH2	*NPM1*	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*
NUP98	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*	*PBRM1*
PC	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*
PTPN11	*PTPN2*	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*
RARA	*RASGEF1A*	*RB1*	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*S1PR2*	*SDHA*	*SDHB*	*SDHC*	*SDHD*
SERP2	*SETBP1*	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA1*
SMARCA4	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*	*SOCS1*	*SOCS2*	*SOCS3*
SOX10	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*	*STAG2*	*STAT3*
STAT4	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*	*TAF1*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	*TMSB4XP8 (TMSL3)*
TNFAIP3	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*	*TRAF2*
TRAF3	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*
U2AF2	*VHL*	*WDR90*	*WHSC1 (MMSET or NSD2)*	*WISP3*	*WT1*	*XBP1*	*XPO1*
YY1AP1	*ZMYM3*	*ZNF217*	*ZNF24 (ZSCAN3)*	*ZNF703*	*ZRSR2*		

*Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR

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HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26 (GRAF)*	
ARHGEF12	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*	*BCL10*	*BCL11A*
BCL11B	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*	*BCR*	*BIRC3*
BRAF	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CHIC2*	*CHN1*	*CIC*	*CIITA*	*CLP1*
CLTC	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*
CTNNB1	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*	*EGFR*	*EIF4A2*	*ELF4*
ELL	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*
FGFR1OP	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*	*FOXO4*	*FOXP1*
FSTL3	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*	*HEY1*	*HIP1*
HIST1H4I	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*	*HOXA9*	*HOXC11*
HOXC13	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*	*IGL*	*IKZF1*
IL21R	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*	*JAZF1*	*KAT6A (MYST3)*
KDSR	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*	*LPP*	*LYL1*
MAF	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1 (ENL)*	*MLLT10 (AF10)*
MLLT3	*MLLT4 (AF6)*	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*
MYC	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*	*NF2*
NFKB2	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*
NUMA1	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*	*PAFAH1B2*	*PAX3*	*PAX5*
PAX7	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*	*PDE4DIP*	*PDGFB*	*PDGFRA*	*PDGFRB*
PER1	*PHF1*	*PICALM*	*PIM1*	*PLAG1*	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*
PRDM16	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*	*RABEP1*	*RAF1*	*RALGDS*	*RAP1GDS1*
RARA	*RBM15*	*RET*	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*
RUNX1T1 (ETO)	*RUNX2*	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*
SNX29 (RUNDC2A)	*SRSF3*	*SS18*	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*STL*	*SYK*
TAF15	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*
TFG	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*
TPM3	*TPM4*	*TRIM24*	*TRIP11*	*TTL*	*TYK2*	*USP6*	*WHSC1 (MMSET or NSD2)*	
WHSC1L1	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*			

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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The median exon coverage for this sample is 783x

ACCURACY		
Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8 copies	>95.0%
Sensitivity: Microsatellite status	At ≥20% tumor nuclei	97.0%
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite status	Positive Predictive Value (PPV)	>95.0%
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

Assay specifications were determined for pical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne Heme test. For MSI results, confirmatory testing using a validated orthogonal method should be considered.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne Heme test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne Heme samples and is reported as the number of mutations per megabase (Muts/Mb). Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

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ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across more than 250 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne Heme 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 FoundationOne Heme 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 Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme 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.

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 Heme.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme 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

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Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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 with no conflicts), 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 *BAP1, BRCA1, BRCA2, BRIP1, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, 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.

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 2.2.0

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