FOUNDATIONONE®CDx

PATIENT

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

COUNTRY CODE
IL

REPORT DATE

ORDERED TEST #

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 Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

ALK **EML4-ALK fusion (Variant 1)**
CDKN2A/B **loss**

7 Disease relevant genes with no reportable alterations: *EGFR, KRAS, BRAF, MET, ERBB2, RET, ROS1*

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

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

GENOMIC FINDINGS

ALK **-** EML4-ALK fusion (Variant 1)

10 Trials *see p. 8*

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	2A	
Entrectinib		

[ ] *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

CDKN2A/B **-** loss ..... p. 3

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.

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]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Aug 2019). 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].

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
1 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] and anti-PD-1 therapies[22-25]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint 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; 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[22-23,26-36]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[37], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[38], 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[39]. 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[40]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[41-42], several other large studies did find a strong association with increased TMB[43-46]. 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[47]. 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)[41]. 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[48]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[48-49].

FINDING SUMMARY

Tumor mutational 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[50-51] and cigarette smoke in lung cancer[26,52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[53-57], and microsatellite instability (MSI)[53,56-57]. 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[22-23,26-36].

GENE
ALK

ALTERATION
EML4-ALK fusion (Variant 1)

POTENTIAL TREATMENT STRATEGIES

ALK mutations or rearrangements may confer sensitivity to ALK TKIs such as crizotinib[58-59], ceritinib[60], brigatinib[61-62], alectinib[63], lorlatinib[64], and entrectinib[65]. 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%[66]. Lorlatinib also elicited significant clinical activity for patients with NSCLC and intracranial[67] or intrathecal[68] metastases and against resistance mutations associated with progression on first- and second-generation ALK TKIs such as G1202R[69-70]. Crizotinib[71], ceritinib[72], and lorlatinib[73-74] further displayed antitumor activity against ALK+ inflammatory myofibroblastic tumors (IMTs) in Phase 1/2 trials. Crizotinib has also shown clinical activity in ALK-mutated neuroblastoma[75], and both crizotinib[76-77] and lorlatinib exhibited preclinical activity against activating ALK point mutations[78-79]. 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 as well as for 1 patient with ALK F1245V mutant neuroblastoma, 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[65]. A Phase 1/1B trial of entrectinib for children and adolescents with recurrent or refractory solid tumors reported a CR in a patient with infantile fibrosarcoma (IFS) and an ALK fusion, a CR in a patient with neuroblastoma and an ALK F1174L mutation, and a PR in a patient with an inflammatory myofibroblastic tumor (IMT) and an ALK fusion[80]. A Phase 2 trial of the HSP90 inhibitor ganetespib reported PRs for a small number of patients with ALK-rearranged NSCLC[81].

FREQUENCY & PROGNOSIS

ALK rearrangements are frequently observed in lung adenocarcinomas[82-84]. 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[85-91]. ALK protein expression has been associated with poor prognosis in some cancer types, including NSCLC, renal cell carcinoma, and neuroblastoma[92-94]. EML4-ALK fusions have been reported to be a significant indicator of poor prognosis in advanced stage NSCLC[91].

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[95]. Different EML4-ALK variants have been identified in cancer, all of which contain the intracellular tyrosine kinase domain of ALK[96]. 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)[97-100], exon 20 (variant 2, 10-12% of cases)[97-100], exon 6 (variant 3 a/b, 26-44% of cases)[97-98,100-102], exon 15 (variant 4, 2% of cases)[86,103-104], exon 18 (variant 5, 1.6-3% of cases)[99,103], exon 2 (variant 5 a/b, 1-2% of cases)[97,104-106], and exon 17 (variant 8 a/b, less than 1%)[99,103,107]. All of these variants have been characterized as, or are predicted to be, activating and sensitive to ALK inhibitors, including crizotinib and ceritinib[98,101,108]; however, variants 3a/b are less sensitive to crizotinib in vitro[98,100]. 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[100,109-110], other studies have not found correlation between EML4-ALK variants and response to crizotinib in NSCLC[99,102].

GENE
CDKN2A/B

ALTERATION
loss

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[111-114]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[115-116], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[117-123]; 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[124-125], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[126]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[127]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[127-133]. In patients with lung SCC, loss of CDKN2B associated with poor survival in one study[134]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[130,135-137].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[138-139]. 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[129,140]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[141-142]. This alteration is predicted to result in p16INK4a[143-164] loss of function. This alteration is predicted to result in p14ARF[147,164-167] loss of function. The CDKN2B alteration is predicted to inactivate p15INK4b[168].

Alectinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

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) who have progressed on or are intolerant to crizotinib.

GENE ASSOCIATION

Activating ALK alterations may predict sensitivity to alectinib on the basis of extensive clinical evidence in ALK-rearranged NSCLC[169-173] .

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 PFS, 68.4% versus 48.7% (HR=0.47); median PFS was 34.8 months in the alectinib arm and was 10.8 months in the crizotinib arm; median OS was not reached in either arm at 2 years[63,174] . Exploratory subgroup analysis of this study, reported improved PFS for patients with EML4-ALK variants 1, 2, and 3a/b when treated with alectinib versus crizotinib in the first line setting[174]. Similar results have been reported in the J-ALEX trial for inhibitor-naive Japanese patients with ALK-positive NSCLC[175]. Alectinib combined with atezolizumab led to an ORR of 81% (17/21) as first-line treatment for PD-L1 unselected, ALK+ NSCLC[176]. In the context of crizotinib resistance, the Phase 3 ALUR trial for patients with ALK+ NSCLC reported that alectinib significantly improved PFS relative to chemotherapy (7.1 vs. 1.6 months; HR=0.32)[177]. Phase 1/2 and Phase 2 trials of alectinib in ALK-rearranged NSCLC refractory to crizotinib reported ORRs of 45–55%[172-173,178] , with a reported median duration of response of 11.2–17 months[173,178-179] . Alectinib has demonstrated significant activity against central nervous system (CNS) metastases, such as leptomeningeal metastases, for patients with NSCLC[63,169,171-173,178,180-184] . In the ALUR trial, alectinib significantly improved ORR for CNS metastases relative to chemotherapy (54.2% vs. 0%)[177]. In the ALEX study, alectinib showed superior efficacy in CNS compared with crizotinib, with 12-month progression rate with CNS disease of 41.4% versus 9.4% and median duration of response in patients with CNS disease at baseline for 17.3 months versus 5.5 months[63]. A Phase 2 study of alectinib for crizotinib-refractory, ALK-rearranged NSCLC reported 27% of patients achieving a CNS-specific CR, and an overall CNS disease control rate of 83% (95% confidence interval, 74% to 91%)[173].

Brigatinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

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) who have progressed on or are intolerant to crizotinib.

GENE ASSOCIATION

Activating ALK alterations may predict sensitivity to brigatinib based on strong clinical[61,185-186] and preclinical[187-188] evidence.

SUPPORTING DATA

Brigatinib has been studied primarily for the treatment of ALK-rearranged NSCLC[186,189-190] . Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations[61]. In the randomized Phase 2 ALTA study, 222 patients with ALK-rearranged NSCLC who progressed on crizotinib were treated with brigatinib and experienced ORRs of 48-53% (with 5 CR, 4 PR) and PFS rates of 9.2-15.6 months (HR=0.55)[186,189] . A Phase 3 study that assessed the efficacy of brigatinib compared to crizotinib in advanced ALK-positive NSCLC, ALK inhibitor-naïve patients, observed that the PFS rate at 1 year was higher with brigatinib than with crizotinib (67% vs. 43%; HR=0.49; $p < 0.001$) and that the ORR and intracranial response rates were 71% and 78% with brigatinib and 60% and 29% with crizotinib, respectively[190]. In another study, brigatinib also demonstrated activity against brain metastasis of patients with ALK-rearranged NSCLC, with 23% (18/79; 2 CR, 7 PR) of patients in the 90 mg dose arm achieving a mean intracranial PFS of 15.6 months (HR=0.66), although the intracranial PFS was not reached in 18% (13/72, 12 PR) of patients in the 180 mg dose arm of the study[189]. In the expansion stage of a Phase 1/2 study, responses to brigatinib were observed in ALK-rearranged NSCLC cases that were ALK-inhibitor naive (4/4 patients, 100% ORR) or previously treated with crizotinib (31/42 patients, 74% ORR)[61].

Ceritinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

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.

GENE ASSOCIATION

On the basis of strong clinical data demonstrating benefit to patients with NSCLC[60,191-196] , inflammatory myofibroblastic tumors, and anaplastic large cell lymphoma[197], ALK rearrangements may predict sensitivity to ceritinib. In ALK-rearranged NSCLC, responses to ceritinib have been observed in crizotinib-naïve patients[60,191,194] as well as after relapse on crizotinib[60,192-193,195-196] .

SUPPORTING DATA

Ceritinib has been shown to confer clinical benefit in patients with ALK/ROS1-rearranged NSCLC[194,198] . 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[194]. 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[191]. 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[193]. 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%[60]. 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[60,195-196] ; for patients with brain metastases, an intracranial ORR of 39% and duration of response of 12.8 months were achieved[192]. In patients with ALK/ROS1-rearranged NSCLC, ceritinib treatment resulted in confirmed PRs in 73% (19/26) with a DCR of 92%[199]. Case studies have also reported responses to ceritinib in patients with ALK+ NSCLC and ALK missense mutation after disease progression on crizotinib[200] or alectinib[201-202] .

Crizotinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

GENE ASSOCIATION

ALK activation may predict sensitivity to crizotinib. In patients with ALK-rearranged NSCLC, crizotinib improved outcomes in both the first-line[59,203] and second-line[204] 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[75,205-208] .

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[59,109,203-204,209] , ROS1 rearrangements[210-214] , an NTRK1 fusion[215], or MET activation[216-232] . The Phase 3 PROFILE 1014 study for patients with ALK-positive non-squamous NSCLC reported significantly prolonged progression-free survival [PFS, 10.9 vs. 7.0 months, hazard ratio (HR) 0.45] and higher objective response rate (ORR, 74% vs. 45%) with first-line crizotinib compared with pemetrexed and cisplatin or carboplatin[59]. A similar Phase 3 study for East Asian patients confirmed that crizotinib is superior to chemotherapy in this setting (PFS of 11.1 vs. 6.8 months, HR 0.40; ORR of 87.5% vs. 45.6%)[203]. In the ongoing Phase 3 PROFILE 1007 study for patients with ALK-positive advanced NSCLC and prior platinum-based therapy (NCT00932893), crizotinib significantly improved median PFS (7.7 months vs. 3.0 months), ORR (65% vs. 20%), and quality of life as compared with chemotherapy[204,233] . The three Phase 3 studies observed numerical, but not statistically significant, improvement of overall survival (OS) with crizotinib (HR of 0.82-0.90), although most patients (70-89%) crossed over from the chemotherapy groups to crizotinib treatment[59,203,209] . The efficacy of crizotinib in patients with brain metastases has also been examined. Prospective comparison of the intracranial efficacy in patients with stable treated brain metastases included in PROFILE 1014 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[234]. 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% vs. 62% and intracranial ORR of 18% vs. 33% in patients with previously untreated versus previously treated brain metastases[235]. In a retrospective study of patients with brain metastases from ALK-rearranged NSCLC, the majority of whom were treated with radiotherapy and crizotinib, 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[236]. Upon disease progression, further survival benefit can be derived for patients with ALK-positive NSCLC who continue crizotinib treatment[237].

Entrectinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

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.

GENE ASSOCIATION

On the basis of clinical evidence in NSCLC, neuroblastoma, and other solid tumors[65,80,238-239] , 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[65]. 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 in patients with NSCLC (2/4), renal cell carcinoma (1/1), CRC (1/1), inflammatory myofibroblastic tumors (2/2) but not for a patient with an unknown primary tumor[65,80] . 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[65,80,240-243] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[244]. 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[65].

Lorlatinib

Assay findings association

ALK
EML4-ALK fusion (Variant 1)

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.

GENE ASSOCIATION

On the basis of extensive clinical evidence in NSCLC[67-68,70,73,245-248] , case studies in inflammatory myofibroblastic sarcoma[73-74] , and preclinical evidence in multiple cell types[69,78-79,249-250] , 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[64,251] . In a Phase 1 trial for ALK- or ROS1-positive advanced NSCLC, lorlatinib treatment elicited CRs for 7% (3/41), PRs for 39% (16/41), and SD for 20% (8/41) of patients with ALK+ tumors, as well as an ORR of 46% (19/41)[64]. The subset of ALK+ patients in this trial who had been previously treated with ≥2 prior TKIs achieved objective responses of 42% (11/26) from lorlatinib[64]. Lorlatinib also resulted in an ORR of 73% (43/59), 39% (11/28), and 39% (43/111) and intracranial ORR of 68% (25/37), 46% (6/13), and 47% (38/81) for patients with NSCLC previously treated with crizotinib, one prior ALK inhibitor, or 2–3 prior ALK inhibitors, respectively[67]. In the same Phase 1/2 trial, lorlatinib reduced the incidence of first intracranial progression, including for patients with prior CNS metastases[251]. Complete resolution of intrathecal metastases and stabilization of CNS metastases was achieved by a heavily pretreated patient with ALK+ NSCLC following lorlatinib treatment[68], and another heavily pretreated patient with EML4-ALK fusion concurrent with G1202R and R1192P achieved a CR from the inhibitor[247]. For patients whose tumors harbored one or more ALK kinase domain mutations, lorlatinib led to responses for 64% (29/45), including 57% (16/28) for those with the ALK G1202R resistance mutation[252]; G1202 therefore does not appear to represent a major mechanism of lorlatinib resistance[69-70,253] . The combination of lorlatinib and the PD-L1 inhibitor avelumab led to a confirmed response rate of 46% (12 PRs, 1 CR) for the 28 treated patients with ALK+ NSCLC[245]. Lorlatinib is currently being evaluated in the first-line setting for patients with ALK+ NSCLC in a Phase 3 trial (NCT03052608)[254].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

IMPORTANT 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 1)

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

NCT03456076

PHASE 3

A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Participants With ALK Positive Non-Small Cell Lung Cancer

TARGETS
ALK, RET

LOCATIONS: Napoli (Italy), Modena (Italy), Ravenna (Italy), Aviano (Italy), Donostia (Spain), Illinois, Kapitanovka Village (Ukraine), Roma (Italy), Cremona (Italy), Milano (Italy), Majadahonda (Spain), Massachusetts, Moscovskaya Oblast (Russian Federation), Moscow (Russian Federation), Camperdown (Australia), St Leonards (Australia), Pennsylvania, Orbassano (Italy), Townsville (Australia), Woolloongabba (Australia), Pisa (Italy), Perugia (Italy), Melbourne (Australia), Wels (Austria), Wien (Austria), Banja Luka (Bosnia and Herzegovina), Mostar (Bosnia and Herzegovina), Sarajevo (Bosnia and Herzegovina), Tuzla (Bosnia and Herzegovina), Guangzhou City (China), Shanghai (China), Cairo (Egypt), Angers (France), Marseille (France), Montpellier (France), Paris (France), St Quentin (France), Strasbourg (France), Suresnes (France), Chemnitz (Germany), Georgsmarienhütte (Germany), Heidelberg (Germany), Immenhausen (Germany), Paderborn (Germany), Athens (Greece), Thessaloniki (Greece), Budapest (Hungary), Pecs (Hungary), Szolnok (Hungary), Beer Sheva (Israel), Haifa (Israel), Kfar- Saba (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Aichi (Japan), Chiba (Japan), Ehime (Japan), Fukuoka (Japan), Hiroshima (Japan), Hokkaido (Japan), Hyogo (Japan), Kanagawa (Japan), Kumamoto (Japan), Miyagi (Japan), Niigata (Japan), Okayama (Japan), Osaka (Japan), Saitama (Japan), Tokyo (Japan), Wakayama (Japan), Yamaguchi (Japan), Almaty (Kazakhstan), Astana (Kazakhstan), Cheongju-si (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Riga (Latvia), Skopje (North Macedonia), Gdańsk (Poland), Kraków (Poland), Olsztyn (Poland), Poznan (Poland), Warszawa (Poland), Coimbra (Portugal), Lisboa (Portugal), Porto (Portugal), Vila Nova De Gaia (Portugal), Krasnodar (Russian Federation), Novosibirsk (Russian Federation), St. Petersburg (Russian Federation), Riyadh (Saudi Arabia), Singapore (Singapore), Durban (South Africa), Barcelona (Spain), La Coruña (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Valencia (Spain), Kaohsiung (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Bangkok (Thailand), ChiangMai (Thailand), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey), Malatya (Turkey), Samsun (Turkey), Dnipropetrovsk (Ukraine), Kyiv (Ukraine), Sumy (Ukraine), Vinnytsia (Ukraine), London (United Kingdom), Manchester (United Kingdom), Preston (United Kingdom)

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: Pessac (France), Mesogeion (Greece), Athens (Greece), Cholargos (Greece), Nea Kifisia (Greece), Heidelberg (Germany), Bangkok (Thailand), Badalona (Spain), Gauting (Germany), Immenstadt (Germany), Beijing (China), Haidian (China), California, Klagenfurt (Austria), Ciudad de Mexico (Mexico), Cheongju-si (Korea, Republic of), Cluj-Napoca (Romania), Dubrovnik (Croatia), Chai Wan (Hong Kong), Meldola (Italy), Georgia, Guangzhou (China), Goyang-si (Korea, Republic of), Incheon (Korea, Republic of), Suwon (Korea, Republic of), Suwon-si (Korea, Republic of), Ulsan (Korea, Republic of), Zhengzhou (China), Creteil (France), Suresnes (France), Villejuif cedex (France), Changchun (China), A Coruna (Spain), Toulouse Cedex 9 (France), New York, Halifax (Canada), Toronto (Canada), Le Mans Cedex 9 (France), Aviano (Italy), Toulon (France), Grenoble Cedex 9 (France), Saint-Petersburg (Russian Federation), Recoleta (Chile), Shanghai (China), Solna (Sweden), Larissa (Greece), Timisoara (Romania), San Miguel De Tucuman (Argentina), Virginia, Hangzhou (China), Cordoba (Argentina), La Rioja (Argentina), Pula (Croatia), Zagreb (Croatia), Central (Hong Kong), Hong Kong (Hong Kong), Kowloon (Hong Kong), Bologna (Italy), Genova (Italy), Milano (Italy), Napoli (Italy), Ravenna (Italy), Seoul (Korea, Republic of), Aguascalientes (Mexico), Bucuresti (Romania), Iasi (Romania), Moscow (Russian Federation), Saint Petersburg (Russian Federation), Barcelona (Spain), Madrid (Spain), Uppsala (Sweden), Changhua City (Taiwan), Hualien City (Taiwan), Kaohsiung (Taiwan), Tainan (Taiwan), Tainan City (Taiwan), Taipei (Taiwan), Songkhla (Thailand)

NCT03052608

PHASE 3

A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC

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

LOCATIONS: L'Hospitalet de Llobregat (Spain), L'Hospitatel De Llobregat (Spain), Pergamino (Argentina), Catania (Italy), Changchun (China), Kislino, Ryshkovsky Rural Council (Russian Federation), Monza (Italy), Milano (Italy), Rozzano (Italy), Majadahonda (Spain), Omsk (Russian Federation), Toronto (Canada), Perugia (Italy), Aviano (Italy), Montreal (Canada), Roma (Italy), Pesochniy Poselok (Russian Federation), Pushkin (Russian Federation), Shanghai (China), Taipei (Taiwan), Melbourne (Australia), Parkville (Australia), Hangzhou (China), Caba (Argentina), Guangzhou (China), Olomouc (Czechia), Praha 2 (Czechia), Praha2 (Czechia), Le Mans (France), Marseille (France), Marseille cedex 09 (France), Marseille cedex 20 (France), Dresden (Germany), Heidelberg (Germany), Regensburg (Germany), Napoli (Italy), Seoul (Korea, Republic of), Ulsan (Korea, Republic of), Aguascalientes (Mexico), Distrito Federal (Mexico), Groningen (Netherlands), Gdansk (Poland), Poznan (Poland), Szczecin (Poland), Warszawa (Poland), Kursk (Russian Federation), Moscow (Russian Federation), A Coruna (Spain), Barcelona (Spain), Girona (Spain), Madrid (Spain)

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: Arizona, California, Napoli (Italy), Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Roma (Italy), Milano (Italy), Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nevada, Liverpool (Australia), New Lambton Heights (Australia), New York, North Carolina, Ohio, Oregon, Candiolo (Italy), Bedford Park (Australia), Texas, Pisa (Italy), Perugia (Italy), Utah, Padova (Italy), Heidelberg (Australia), Virginia, Washington, Edegem (Belgium), Shanghai (China), Angers (France), Bordeaux (France), Lille (France), Lyon (France), Marseille (France), Marseille cedex 5 (France), Montpellier cedex 5 (France), Paris (France), Saint Herblain (France), Toulouse (France), Villejuif cedex (France), Berlin (Germany), Dresden (Germany), Göttingen (Germany), Heidelberg (Germany), Köln (Germany), Hong Kong (Hong Kong), Kowloon (Hong Kong), Shatin (Hong Kong), Aichi (Japan), Ehime (Japan), Fukuoka (Japan), Hyogo (Japan), Kashiwa-shi (Japan), Miyagi (Japan), Niigata (Japan), Osaka (Japan), Shizuoka (Japan), Seoul (Korea, Republic of), Amsterdam (Netherlands), Leiden (Netherlands), Gdańsk (Poland), Gliwice (Poland), Poznań (Poland), Warszawa (Poland), Singapore (Singapore), Barcelona (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Tainan (Taiwan), Taipei (Taiwan), Taipei City (Taiwan), Cambridge (United Kingdom), London (United Kingdom), Manchester (United Kingdom)

NCT03535740

PHASE 2

A Study of Brigatinib in Participants With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

TARGETS
ALK, EGFR, ROS1

LOCATIONS: Toyoake (Japan), Edmonton (Canada), Pessac (France), Heidelberg (Germany), Ulm (Germany), Badalona (Spain), Kempten (Germany), Munchen (Germany), Beijing (China), Calgary (Canada), California, Klagenfurt (Austria), Changhua City (Taiwan), Colorado, Florida, Guangzhou (China), Goyang-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Cheongju-si (Korea, Republic of), Creteil (France), Changchun (China), Yokohama (Japan), A Coruna (Spain), Roma (Italy), Maastricht (Netherlands), Michigan, Toulouse Cedex 9 (France), Missouri, Sendai (Japan), Shatin (Hong Kong), Oldenburg (Germany), Amsterdam (Netherlands), Hamm (Germany), North Carolina, Okayama-city (Japan), Toronto (Canada), Oregon, Hirakata-shi (Japan), Aviano (Italy), Marseille (France), Montreal (Canada), Lyon (France), Shanghai (China), Lund (Sweden), Tainan (Taiwan), Tennessee, Koto-ku (Japan), Orbassano (Italy), Linz (Austria), Fitzroy (Australia), Frankston (Australia), Virginia, Nedlands (Australia), Hangzhou (China), Rotterdam (Netherlands), Berlin (Germany), Hong Kong (Hong Kong), Kowloon (Hong Kong), Milano (Italy), Napoli (Italy), Parma (Italy), Ravenna (Italy), Daegu (Korea, Republic of), Barcelona (Spain), Madrid (Spain), Stockholm (Sweden), Uppsala (Sweden), Taichung (Taiwan)

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: Edmonton (Canada), California, Singapore (Singapore), Cheongju-si (Korea, Republic of), Colorado, District of Columbia, Florida, Georgia, Massachusetts, Michigan, Minnesota, Missouri, New Jersey, Camperdown (Australia), New York, Ohio, Texas, Melbourne (Australia), Virginia, Washington, Seoul (Korea, Republic of), Groningen (Netherlands), Manchester (United Kingdom)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Belfast (United Kingdom), Birmingham (United Kingdom), Bristol (United Kingdom), Cambridge (United Kingdom), Cardiff (United Kingdom), Colchester (United Kingdom), Exeter (United Kingdom), Glasgow (United Kingdom), Leeds (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle (United Kingdom), Oxford (United Kingdom), Sheffield (United Kingdom), Southampton (United Kingdom)

NCT02314481

PHASE 2

Deciphering Antitumour Response and Resistance With Intratumour Heterogeneity - DARWIN II

TARGETS
PD-L1, BRAF, ALK, RET, ERBB2

LOCATIONS: London (United Kingdom)

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: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming

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: Arizona, Arkansas, California, Colorado, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington, Wisconsin, Wyoming

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.

ALK loss	***ATM*** L2307F	***CALR*** Y57C	***FANCA*** T126R
IGF1R N202S	***NF1*** H1814Y	***SPEN*** R140G	

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)

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.

NCCN Categorization

Biomarker and genomic findings detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories 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.

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 defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
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.

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

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1. Gatalica Z, Snyder C, Maney T, et al. ePub Dec 2014 (2014) PMID: 25392179
2. Kroemer G, Galluzzi L, Zitvogel L, et al. 4 (7):e1058597 (2015) PMID: 26140250
3. Lal N, Beggs AD, Willcox BE, et al. 4 (3):e976052 (2015) PMID: 25949894
4. Le DT, Uram JN, Wang H, et al. ePub Jun 2015 (2015) PMID: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, Körner S, Penzel R, et al. ePub Mar 2016 (2016) PMID: 26637197
7. Ninomiya H, Nomura K, Satoh Y, et al. 94 (10):1485-91 (2006) PMID: 16641899
8. Vanderwalde A, Spetzler D, Xiao N, et al. ePub 03 2018 (2018) PMID: 29436178
9. Zang YS, Dai C, Xu X, et al. ePub Jul 2019 (2019) PMID: 31270941
10. Dudley JC, Lin MT, Le DT, et al. 22 (4):813-20 (2016) PMID: 26880610
11. Takamochi K, Takahashi F, Suehara Y, et al. ePub 08 2017 (2017) PMID: 28676214
12. Pylkkänen L, Karjalainen A, Anttila S, et al. 30 (2):217-23 (1997) PMID: 9329646
13. Gonzalez R, Silva JM, Sanchez A, et al. 11 (9):1097-104 (2000) PMID: 11061602
14. Chen XQ, Stroun M, Magnenat JL, et al. 2 (9):1033-5 (1996) PMID: 8782463
15. Merlo A, Mabry M, Gabrielson E, et al. 54 (8):2098-101 (1994) PMID: 8174113
16. Kocarnik JM, Shiovitz S, Phipps AI 3 (4):269-76 (2015) PMID: 26337942
17. You JF, Buhard O, Ligtenberg MJ, et al. ePub Dec 2010 (2010) PMID: 21081928
18. Bairwa NK, Saha A, Gochhait S, et al. ePub 2014 (2014) PMID: 24623249
19. Boland CR, Thibodeau SN, Hamilton SR, et al. 58 (22):5248-57 (1998) PMID: 9823339
20. Pawlik TM, Raut CP, Rodriguez-Bigas MA 20 (4-5):199-206 (2004) PMID: 15528785
21. Boland CR, Goel A ePub Jun 2010 (2010) PMID: 20420947
22. Samstein RM, Lee CH, Shoushtari AN, et al. ePub 02 2019 (2019) PMID: 30643254
23. Goodman AM, Kato S, Bazhenova L, et al. ePub 11 2017 (2017) PMID: 28835386
24. Goodman AM, Sokol ES, Frampton GM, et al. ePub Oct 2019 (2019) PMID: 31405947
25. Cristescu R, Mogg R, Ayers M, et al. ePub 10 2018 (2018) PMID: 30309915
26. Rizvi NA, Hellmann MD, Snyder A, et al. ePub Apr 2015 (2015) PMID: 25765070
27. Colli LM, Machiela MJ, Myers TA, et al. ePub 07 2016 (2016) PMID: 27197178
28. Wang VE, Urisman A, Albacker L, et al. ePub 09 2017 (2017) PMID: 28923100
29. Carbone DP, Reck M, Paz-Ares L, et al. ePub 06 2017 (2017) PMID: 28636851
30. Rizvi H, Sanchez-Vega F, La K, et al. ePub Mar 2018 (2018) PMID: 29337640
31. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. ePub 05 2018 (2018) PMID: 29658845
32. Hellmann MD, Nathanson T, Rizvi H, et al. ePub May 2018 (2018) PMID: 29657128
33. Forde PM, Chaft JE, Smith KN, et al. ePub 05 2018 (2018) PMID: 29658848
34. Ready N, Hellmann MD, Awad MM, et al. ePub Apr 2019 (2019) PMID: 30785829
35. Miao D, Margolis CA, Vokes NI, et al. ePub Sep 2018 (2018) PMID: 30150660
36. Chae YK, Davis AA, Raparia K, et al. ePub 03 2019 (2019) PMID: 30425022
37. Paz-Ares et al., 2019; ESMO Abstract LBA80
38. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. ePub Sep 2019 (2019) PMID: 31562796
39. Chalmers ZR, Connelly CF, Fabrizio D, et al. ePub 04 2017 (2017) PMID: 28420421
40. Spigel et al., 2016; ASCO Abstract 9017
41. Xiao D, Pan H, Li F, et al. ePub Apr 2016 (2016) PMID: 27009843
42. Shim HS, Kenudson M, Zheng Z, et al. ePub Aug 2015 (2015) PMID: 26200269
43. Govindan R, Ding L, Griffith M, et al. ePub Sep 2012 (2012) PMID: 22980976
44. Ding L, Getz G, Wheeler DA, et al. ePub Oct 2008 (2008) PMID: 18948947
45. Imielinski M, Berger AH, Hammerman PS, et al. ePub Sep 2012 (2012) PMID: 22980975
46. Kim Y, Hammerman PS, Kim J, et al. ePub Jan 2014 (2014) PMID: 24323028
47. Stein et al., 2019; DOI: 10.1200/PO.18.00376
48. Chen Y, Liu Q, Chen Z, et al. ePub May 2019 (2019) PMID: 31088500
49. Yu H, Chen Z, Ballman KV, et al. ePub 01 2019 (2019) PMID: 30253973
50. Pfeifer GP, You YH, Besaratinia A 571 (1-2):19-31 (2005) PMID: 15748635
51. Hill VK, Gartner JJ, Samuels Y, et al. ePub 2013 (2013) PMID: 23875803
52. Pfeifer GP, Denissenko MF, Olivier M, et al. 21 (48):7435-51 (2002) PMID: 12379884
53. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. ePub May 2013 (2013) PMID: 23636398
54. Briggs S, Tomlinson I ePub Jun 2013 (2013) PMID: 23447401
55. Heitzer E, Tomlinson I ePub Feb 2014 (2014) PMID: 24583393
56. null ePub Jul 2012 (2012) PMID: 22810696
57. Roberts SA, Gordenin DA ePub 12 2014 (2014) PMID: 25568919
58. Solomon BJ, Kim DW, Wu YL, et al. ePub Aug 2018 (2018) PMID: 29768118
59. Solomon BJ, Mok T, Kim DW, et al. ePub Dec 2014 (2014) PMID: 25470694
60. Kim DW, Mehra R, Tan DSW, et al. ePub Apr 2016 (2016) PMID: 26973324
61. Gettinger SN, Bazhenova LA, Langer CJ, et al. ePub Dec 2016 (2016) PMID: 27836716
62. Camidge DR, Kim DW, Tiseo M, et al. ePub Sep 2018 (2018) PMID: 29768119
63. Peters S, Camidge DR, Shaw AT, et al. ePub 08 2017 (2017) PMID: 28586279
64. Shaw AT, Felip E, Bauer TM, et al. ePub Dec 2017 (2017) PMID: 29074098
65. Drilon A, Siena S, Ou SI, et al. ePub 04 2017 (2017) PMID: 28183697
66. Camidge et al., 2019; ESMO Abstract 1487PD
67. Besse et al., 2018; ASCO Abstract 9032
68. Hochmair MJ, Schwab S, Prosch H ePub 09 2017 (2017) PMID: 28628492
69. Yoda S, Lin JJ, Lawrence MS, et al. ePub Jun 2018 (2018) PMID: 29650534
70. Dagogo-Jack I, Brannon AR, Ferris LA, et al. 2018 (2018) PMID: 29376144
71. Schöffski P, Sufliarsky J, Gelderblom H, et al. ePub Jun 2018 (2018) PMID: 29669701
72. Nishio M, Murakami H, Horiike A, et al. ePub Jul 2015 (2015) PMID: 26020125
73. Yuan C, Ma MJ, Parker JV, et al. ePub Jul 2017 (2017) PMID: 28713152
74. Parker BM, Parker JV, Lymperopoulos A, et al. ePub Jan 2018 (2018) PMID: 29925295
75. Mossé YP, Lim MS, Voss SD, et al. ePub May 2013 (2013) PMID: 23598171
76. Chand D, Yamazaki Y, Ruuth K, et al. ePub Mar 2013 (2013) PMID: 23104988
77. Schönherr C, Ruuth K, Yamazaki Y, et al. ePub Dec 2011 (2011) PMID: 21838707
78. Zou HY, Friboulet L, Kodack DP, et al. ePub Jul 2015 (2015) PMID: 26144315
79. Infarinato NR, Park JH, Krytska K, et al. ePub Jan 2016 (2016) PMID: 26554404
80. Robinson et al., 2019; ASCO Abstract 10009
81. Socinski MA, Goldman J, El-Hariry I, et al. 19 (11):3068-77 (2013) PMID: 23553849
82. To KF, Tong JH, Yeung KS, et al. ePub Jul 2013 (2013) PMID: 23625156
83. Selinger CI, Rogers TM, Russell PA, et al. ePub Dec 2013 (2013) PMID: 23743928
84. Takeuchi K, Choi YL, Togashi Y, et al. 15 (9):3143-9 (2009) PMID: 19383809
85. Inamura K, Takeuchi K, Togashi Y, et al. ePub Apr 2009 (2009) PMID: 19234440
86. Koivunen JP, Mermel C, Zejnullahu K, et al. 14 (13):4275-83 (2008) PMID: 18594010
87. Shaw AT, Yeap BY, Mino-Kenudson M, et al. ePub Sep 2009 (2009) PMID: 19667264
88. Takahashi T, Sonobe M, Kobayashi M, et al. ePub Mar 2010 (2010) PMID: 20183914
89. Li Y, Li Y, Yang T, et al. ePub 2013 (2013) PMID: 23341890
90. Li H, Pan Y, Li Y, et al. ePub Jan 2013 (2013) PMID: 23098378
91. Zhou JX, Yang H, Deng Q, et al. ePub May 2013 (2013) PMID: 23277484
92. Takeda M, Okamoto I, Sakai K, et al. ePub Nov 2012 (2012) PMID: 22771825
93. Sukov WR, Hodge JC, Lohse CM, et al. ePub Nov 2012 (2012) PMID: 22743654
94. Duijkers FA, Gaal J, Meijerink JP, et al. ePub Mar 2012 (2012) PMID: 22203052
95. Grande E, Bolós MV, Arriola E ePub Apr 2011 (2011) PMID: 21474455
96. Peters S, Taron M, Bubendorf L, et al. ePub Aug 2013 (2013) PMID: 23769207
97. Li T, Maus MK, Desai SJ, et al. ePub Jan 2014 (2014) PMID: 24346090
98. Heuckmann JM, Balke-Want H, Malchers F, et al. 18 (17):4682-90 (2012) PMID: 22912387
99. Lei YY, Yang JJ, Zhang XC, et al. ePub 05 2016 (2016) PMID: 26454342
100. Woo CG, Seo S, Kim SW, et al. ePub 04 2017 (2017) PMID: 28039177
101. Choi YL, Takeuchi K, Soda M, et al. ePub Jul 2008 (2008) PMID: 18593892
102. Kwak EL, Bang YJ, Camidge DR, et al. ePub Oct 2010 (2010) PMID: 20979469
103. Sasaki T, Rodig SJ, Chirieac LR, et al. ePub Jul 2010 (2010) PMID: 20418096

104. Takeuchi K, Choi YL, Soda M, et al. 14 (20):6618-24 (2008) PMID: 18927303

105. Zhang X, Zhang S, Yang X, et al. ePub Jul 2010 (2010) PMID: 20624322

106. Maus MK, Stephens C, Zeger G, et al. 8 (1):1-6 (2012) PMID: 23675251

107. Sanders HR, Li HR, Bruey JM, et al. 204 (1):45-52 (2011) PMID: 21356191

108. Soda M, Choi YL, Enomoto M, et al. ePub Aug 2007 (2007) PMID: 17625570

109. Yoshida T, Oya Y, Tanaka K, et al. ePub Oct 2016 (2016) PMID: 27354483

110. Seo S, Woo CG, Lee DH, et al. ePub 07 2017 (2017) PMID: 28407036

111. Konecny GE, Winterhoff B, Kolarova T, et al. 17 (6):1591-602 (2011) PMID: 21278246

112. Katsumi Y, Iehara T, Miyachi M, et al. ePub Sep 2011 (2011) PMID: 21871868

113. Cen L, Carlson BL, Schroeder MA, et al. ePub Jul 2012 (2012) PMID: 22711607

114. Logan JE, Mostofizadeh N, Desai AJ, et al. ePub Aug 2013 (2013) PMID: 23898052

115. Elvin JA, Gay LM, Ort R, et al. ePub 04 2017 (2017) PMID: 28283584

116. Gao J, Adams RP, Swain SM 22 (6):e498-501 (2015) PMID: 26715889

117. Gopalan et al., 2014; ASCO Abstract 8077

118. Peguero et al., 2016; ASCO Abstract 2528

119. Konecny et al., 2016; ASCO Abstract 5557

120. DeMichele A, Clark AS, Tan KS, et al. 21 (5):995-1001 (2015) PMID: 25501126

121. Finn RS, Crown JP, Lang I, et al. ePub Jan 2015 (2015) PMID: 25524798

122. Infante JR, Cassier PA, Gerecitano JF, et al. 22 (23):5696-5705 (2016) PMID: 27542767

123. Johnson DB, Dahlman KH, Knol J, et al. ePub Jun 2014 (2014) PMID: 24797823

124. Van Maerken T, Rihani A, Dreidax D, et al. ePub Jun 2011 (2011) PMID: 21460101

125. Gamble LD, Kees UR, Tweddle DA, et al. ePub Feb 2012 (2012) PMID: 21725357

126. null ePub Jul 2014 (2014) PMID: 25079552

127. null ePub Sep 2012 (2012) PMID: 22960745

128. Doxtader EE, Katzenstein AL ePub Mar 2012 (2012) PMID: 21840041

129. Gazzeri S, Gouyer V, Vour'ch C, et al. 16 (4):497-504 (1998) PMID: 9484839

130. Kratzke RA, Greatens TM, Rubins JB, et al. 56 (15):3415-20 (1996) PMID: 8758904

131. Lee JU, Sul HJ, Son JW ePub Jul 2012 (2012) PMID: 23101020

132. Cortot AB, Younes M, Martel-Planche G, et al. ePub Mar 2014 (2014) PMID: 24169260

133. Mounawar M, Mukeria A, Le Calvez F, et al. 67 (12):5667-72 (2007) PMID: 17575133

134. Zhao Y, Li Y, Lu H, et al. ePub Sep 2011 (2011) PMID: 21889114

135. Kawabuchi B, Moriyama S, Hironaka M, et al. 84 (1):49-53 (1999) PMID: 9988232

136. Xing XB, Cai WB, Luo L, et al. ePub 2013 (2013) PMID: 23805242

137. Lou-Qian Z, Rong Y, Ming L, et al. ePub 2013 (2013) PMID: 23372805

138. Quelle DE, Zindy F, Ashmun RA, et al. 83 (6):993-1000 (1995) PMID: 8521522

139. null 576 (1-2):22-38 (2005) PMID: 15878778

140. null 18 (38):5311-7 (1999) PMID: 10498883

141. Sherr CJ, Bertwistle D, DEN Besten W, et al. 70 :129-37 (2005) PMID: 16869746

142. Ozenne P, Eymin B, Brambilla E, et al. ePub Nov 2010 (2010) PMID: 20549699

143. Ruas M, Brookes S, McDonald NQ, et al. 18 (39):5423-34 (1999) PMID: 10498896

144. Jones R, Ruas M, Gregory F, et al. 67 (19):9134-41 (2007) PMID: 17909018

145. Haferkamp S, Becker TM, Scurr LL, et al. ePub Oct 2008 (2008) PMID: 18843795

146. Huot TJ, Rowe J, Harland M, et al. 22 (23):8135-43 (2002) PMID: 12417717

147. Rizos H, Darmanian AP, Holland EA, et al. 276 (44):41424-34 (2001) PMID: 11518711

148. Gombart AF, Yang R, Campbell MJ, et al. 11 (10):1673-80 (1997) PMID: 9324288

149. Yang R, Gombart AF, Serrano M, et al. 55 (12):2503-6 (1995) PMID: 7780957

150. Parry D, Peters G 16 (7):3844-52 (1996) PMID: 8668202

151. Greenblatt MS, Beaudet JG, Gump JR, et al. 22 (8):1150-63 (2003) PMID: 12606942

152. Yarbrough WG, Buckmire RA, Bessho M, et al. 91 (18):1569-74 (1999) PMID: 10491434

153. Poi MJ, Yen T, Li J, et al. 30 (1):26-36 (2001) PMID: 11255261

154. Byeon IJ, Li J, Ericson K, et al. 1 (3):421-31 (1998) PMID: 9660926

155. Kannengiesser C, Brookes S, del Arroyo AG, et al. ePub Apr 2009 (2009) PMID: 19260062

156. Lal G, Liu L, Hogg D, et al. 27 (4):358-61 (2000) PMID: 10719365

157. Koh J, Enders GH, Dynlacht BD, et al. 375 (6531):506-10 (1995) PMID: 7777061

158. McKenzie HA, Fung C, Becker TM, et al. ePub Jun 2010 (2010) PMID: 20340136

159. Miller PJ, Duraisamy S, Newell JA, et al. ePub Aug 2011 (2011) PMID: 21462282

160. Kutscher CL, Wright WA 18 (1):87-94 (1977) PMID: 905385

161. Scaini MC, Minervini G, Elefanti L, et al. ePub Jul 2014 (2014) PMID: 24659262

162. Jenkins NC, Jung J, Liu T, et al. ePub Apr 2013 (2013) PMID: 23190892

163. Walker GJ, Gabrielli BG, Castellano M, et al. 82 (2):305-12 (1999) PMID: 10389768

164. Rutter JL, Goldstein AM, Dávila MR, et al. 22 (28):4444-8 (2003) PMID: 12853981

165. Itahana K, Zhang Y ePub Jun 2008 (2008) PMID: 18538737

166. Zhang Y, Xiong Y 3 (5):579-91 (1999) PMID: 10360174

167. Zhang Y, Xiong Y, Yarbrough WG 92 (6):725-34 (1998) PMID: 9529249

168. Jafri M, Wake NC, Ascher DB, et al. ePub Jul 2015 (2015) PMID: 25873077

169. Ohe et al., 2015; ASCO Abstract 8061

170. Gandhi et al., 2015; ASCO Abstract 8019

171. Seto T, Kiura K, Nishio M, et al. ePub Jun 2013 (2013) PMID: 23639470

172. Gadgeel SM, Gandhi L, Riely GJ, et al. ePub Sep 2014 (2014) PMID: 25153538

173. Ou SH, Ahn JS, De Petris L, et al. ePub Mar 2016 (2016) PMID: 26598747

174. Camidge DR, Dziadziuszko R, Peters S, et al. ePub Jul 2019 (2019) PMID: 30902613

175. Hida T, Nokihara H, Kondo M, et al. ePub 07 2017 (2017) PMID: 28501140

176. Kim et al., 2018; ASCO Abstract 9009

177. Novello S, Mazières J, Oh IJ, et al. ePub Jun 2018 (2018) PMID: 29668860

178. Shaw AT, Gandhi L, Gadgeel S, et al. ePub Feb 2016 (2016) PMID: 26708155

179. Lin et al., 2018; ASCO Abstract 9093

180. Gainor JF, Sherman CA, Willoughby K, et al. ePub Feb 2015 (2015) PMID: 25526238

181. Ajimizu H, Kim YH, Mishima M ePub Feb 2015 (2015) PMID: 25556163

182. Ou SH, Sommers KR, Azada MC, et al. ePub Feb 2015 (2015) PMID: 25568147

183. Klempner SJ, Ou SH ePub Jun 2015 (2015) PMID: 26112806

184. Dempke WC, Edvardsen K, Lu S, et al. ePub Nov 2015 (2015) PMID: 26504000

185. Kim et al., 2016; ASCO Abstract 9007

186. Camidge et al., 2016; World Conference on Lung Cancer P3.02a-013

187. Zhang S, Anjum R, Squillace R, et al. 22 (22):5527-5538 (2016) PMID: 27780853

188. Siaw JT, Wan H, Pfeifer K, et al. ePub May 2016 (2016) PMID: 27049722

189. Kim DW, Tiseo M, Ahn MJ, et al. ePub Aug 2017 (2017) PMID: 28475456

190. Camidge DR, Kim HR, Ahn MJ, et al. ePub Sep 2018 (2018) PMID: 30280657

191. Felip et al., 2015; ASCO Abstract 8060

192. Felip et al., 2015; ELCC Abstract 141PD

193. Scagliotti et al., 2016; ESMO Abstract LBA42_PR

194. Soria JC, Tan DSW, Chiari R, et al. ePub 03 2017 (2017) PMID: 28126333

195. Crinò L, Ahn MJ, De Marinis F, et al. ePub Aug 2016 (2016) PMID: 27432917

196. Shaw AT, Kim DW, Mehra R, et al. ePub Mar 2014 (2014) PMID: 24670165

197. Geoerger et al., 2015; ASCO Abstract 10005

198. Lim SM, Kim HR, Lee JS, et al. ePub Aug 2017 (2017) PMID: 28520527

199. Wu et al., 2018; WCLC Abstract P1.01-97

200. Kodityal S, Elvin JA, Squillace R, et al. ePub Feb 2016 (2016) PMID: 26775591

201. Katayama R, Friboulet L, Koike S, et al. 20 (22):5686-96 (2014) PMID: 25228534

202. Ou SH, Greenbowe J, Khan ZU, et al. ePub May 2015 (2015) PMID: 25736571

203. Lu et al., 2016; ASCO Abstract 9058

204. Shaw AT, Kim DW, Nakagawa K, et al. ePub Jun 2013 (2013) PMID: 23724913

205. Brugieres et al., 2017; ASH Abstract 2831

206. Gambacorti-Passerini et al., 2017; ASH Abstract 4128

207. Butrynski JE, D'Adamo DR, Hornick JL, et al. ePub Oct 2010 (2010) PMID: 20979472

208. Pérot G, Soubeyran I, Ribeiro A, et al. ePub 2014 (2014) PMID: 24475247

209. Shaw et al., 2016; ASCO Abstract 9066

210. Moro-Sibilot D, Cozic N, Pérol M, et al. ePub Dec 2019 (2019) PMID: 31584608

211. Goto et al., 2016; ASCO Abstract 9022

212. Shaw AT, Ou SH, Bang YJ, et al. ePub Nov 2014 (2014) PMID: 25264305

213. Mazières J, Zalcman G, Crinò L, et al. ePub Mar 2015 (2015) PMID: 25667280

214. Scheffler M, Schultheis A, Teixido C, et al. ePub Apr 2015 (2015) PMID: 25868855

215. Vaishnavi A, Capelletti M, Le AT, et al. ePub Nov 2013 (2013) PMID: 24162815

216. Drilon et al., 2016; ASCO Abstract 108

217. Vassal et al., 2015; ASCO Abstract 2595

218. Camidge et al., 2014; ASCO Abstract 8001

219. Li et al., 2015; ASCO Abstract 8090

220. Schrock AB, Frampton GM, Suh J, et al. ePub 09 2016 (2016) PMID: 27343443

221. Jorge SE, Schulman S, Freed JA, et al. ePub Dec 2015 (2015) PMID: 26791794

222. Paik PK, Drilon A, Fan PD, et al. ePub Aug 2015 (2015) PMID: 25971939

223. Mahjoubi L, Gazzah A, Besse B, et al. ePub 06 2016 (2016) PMID: 26892698

224. Benderra MA, Aspeslagh S, Postel-Vinay S, et al. ePub Feb 2016 (2016) PMID: 26845121

225. Waqar SN, Morgensztern D, Sehn J ePub May 2015 (2015) PMID: 25898962

226. Mendenhall MA, Goldman JW ePub May 2015 (2015) PMID: 25898965

227. Jenkins RW, Oxnard GR, Elkin S, et al. ePub Sep 2015 (2015) PMID: 25769807

228. Awad MM, Oxnard GR, Jackman DM, et al. ePub Mar 2016 (2016) PMID: 26729443

229. Schwab R, Petak I, Kollar M, et al. ePub Jan 2014 (2014) PMID: 24192513

230. Zhang Y, Wang W, Wang Y, et al. ePub 05 2016 (2016) PMID: 26724472

231. Ou SH, Kwak EL, Siwak-Tapp C, et al. ePub May 2011 (2011) PMID: 21623265

232. Le X, Freed JA, VanderLaan PA, et al. ePub Sep 2015 (2015) PMID: 25922291

233. Blackhall F, Kim DW, Besse B, et al. ePub Nov 2014 (2014) PMID: 25436797

234. Solomon BJ, Cappuzzo F, Felip E, et al. ePub Aug 2016 (2016) PMID: 27022118

235. Costa DB, Shaw AT, Ou SH, et al. ePub Jun 2015 (2015) PMID: 25624436

236. Johung KL, Yeh N, Desai NB, et al. ePub Jan 2016 (2016) PMID: 26438117

237. Ou SH, Jänne PA, Bartlett CH, et al. ePub Feb 2014 (2014) PMID: 24478318

238. Desai et al., 2018; ASCO Abstract 10536

239. Ambati et al., 2018; doi/full/10.1200/PO.18.00095

240. Demetri et al., 2018; ESMO Abstract LBA17

241. Siena et al., 2019; ASCO Abstract 3017

242. Doebele et al., 2019; ASCO Abstract 9070

243. Doebele et al., 2018; WCLC Abstract OA02.01

244. Smith KM, Fagan PC, Pomari E, et al. ePub 02 2018 (2018) PMID: 29237803

245. Shaw et al., 2018; ASCO Abstract 9008

246. Shaw et al., 2018; AACR Abstract CT044

247. Baglivo S, Ricciuti B, Ludovini V, et al. ePub Aug 2018 (2018) PMID: 30049377

248. Facchinetti F, Gnetti L, Balestra V, et al. ePub Aug 2018 (2018) PMID: 30066208

249. Childress MA, Himmelberg SM, Chen H, et al. ePub Nov 2018 (2018) PMID: 30002191

250. Gainor JF, Dardaei L, Yoda S, et al. ePub 10 2016 (2016) PMID: 27432227

251. Bauer et al., 2018; WCLC Abstract MA08.05

252. Shaw AT, Solomon BJ, Besse B, et al. ePub Jun 2019 (2019) PMID: 30892989

253. Ou SI, Lee TK, Young L, et al. ePub 04 2017 (2017) PMID: 28285684

254. Solomon et al., 2018; IASLC 19th WCLC Abstract P1.13-06