FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung small cell undifferentiated carcinoma

COUNTRY CODE
TR

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 small cell undifferentiated carcinoma
**NAME**
**DATE OF BIRTH**
**SEX**
**MEDICAL RECORD #**

## PHYSICIAN

**ORDERING PHYSICIAN**
**MEDICAL FACILITY**
**ADDITIONAL RECIPIENT**
**MEDICAL FACILITY ID**
**PATHOLOGIST**

## SPECIMEN

**SPECIMEN SITE** Liver
**SPECIMEN ID**
**SPECIMEN TYPE**
**DATE OF COLLECTION**
**SPECIMEN RECEIVED**

## Biomarker Findings

**Tumor Mutational Burden** - 18 Muts/Mb
**Microsatellite status** - MS-Stable

## Genomic Findings

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

***RB1*** K810*
***TP53*** P152fs*18

**6** Therapies with Clinical Benefit
**0** Therapies with Lack of Response
**11** Clinical Trials

### BIOMARKER FINDINGS

**Tumor Mutational Burden** - 18 Muts/Mb

**10 Trials** *see p. 7*

| THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) | | THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) | |
|---|---|---|---|
| Atezolizumab | 1 | Durvalumab | 1 |
| Nivolumab | 2A | Avelumab | |
| Pembrolizumab | 2A | Cemiplimab | |

**Microsatellite status** - MS-Stable

**No therapies or clinical trials.** see Biomarker Findings section

### GENOMIC FINDINGS

***RB1*** - K810*

**1 Trial** *see p. 10*

| THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) |
|---|---|
| none | none |

☐ *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.*

***TP53*** - P152fs*18 ..... 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

# Tumor Mutational Burden

**RESULT**
18 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[1-3] and anti-PD-1 therapies[1-4]. The Phase 1/2 CheckMate 032 trial as well as 2 large-scale retrospective analyses of SCLC reported that patients with tumors harboring TMB ≥13 Muts/Mb experienced higher rates of clinical benefit and longer PFS and OS on treatment with the PD-1 inhibitors pembrolizumab or nivolumab (alone or in combination with ipilimumab) or the PD-L1 inhibitor atezolizumab, compared with patients with tumors with TMB <13 Muts/Mb[5-7].

### FREQUENCY & PROGNOSIS

Small cell lung cancer (SCLC) has been reported to have a median mutational burden of 5-10 mutations per megabase (muts/Mb), and 0-9% of SCLCs have been reported to harbor high TMB (>20 muts/Mb)[8-10]. In one study, large cell neuroendocrine carcinomas (LCNEC) were reported to have an average mutational burden of 10.5 muts/Mb, which was higher than the mutational burden of non-small cell lung cancer (NSCLC) or SCLC[9]. In one study, higher nonsynonymous mutation burden correlated with immune cell infiltration of tumors and higher PD-L1 expression on immune cells in patients with SCLC and LCNEC[11].

### 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[12-13] and cigarette smoke in lung cancer[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. This sample harbors a TMB level that may be associated with sensitivity to treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[5-7].

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[21-23], including approved therapies nivolumab and pembrolizumab[24]. 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)[25].

### FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[26-31], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[32-35]. The prognostic significance of MSI in small cell lung cancer is unknown (PubMed, Jun 2019).

### 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[36]. 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[36-38]. 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[39-41]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[36,38,40-41].

GENE
## *RB1*

**ALTERATION**
K810*

**TRANSCRIPT NUMBER**
NM_000321

**CODING SEQUENCE EFFECT**
2428A>T

### POTENTIAL TREATMENT STRATEGIES

On the basis of limited clinical data[42] and strong preclinical data[43-45], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit[46]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[47] and activation of the NOTCH pathway[48]. Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, or ribociclib, which act upstream of Rb[49-57]. Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer[58-59].

### FREQUENCY & PROGNOSIS

RB1 mutation has been observed in 33-74% of small cell lung cancer (SCLC) cases[60-62]. Inactivation of RB1 and subsequent loss of Rb protein expression is a hallmark molecular event in SCLC, cited in more than 90% of cases in some studies[62-64]. Inactivation of both Rb and p53 in a mouse model led to the development of SCLC tumors, supporting the suggestion that Rb loss is critically involved in SCLC development[65].

### FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[59,63]. RB1 alterations that disrupt or remove the pocket domain (aa 373-771) and/or the C-terminal domain (aa 773-928), such as observed here, are predicted to be inactivating[66-72]. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[73]. Germline mutations in RB1 account for approximately 40% of RB tumors[74] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[75-76]. In the appropriate clinical context, germline testing of RB1 is recommended.

GENE
## *TP53*

**ALTERATION**
P152fs*18

**TRANSCRIPT NUMBER**
NM_000546

**CODING SEQUENCE EFFECT**
455delC

### POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[77-80], or p53 gene therapy and immunotherapeutics such as SGT-53[81-85] and ALT-801[86]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53 wild-type[87]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[88]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[89]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[90]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate in patients with TP53 alterations[91]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[85]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutant, but not TP53-wild-type, breast cancer xenotransplant mouse model[92].

### FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in small cell lung cancer (SCLC), with mutations present in 79-92% of tumors[60-62]. Deletion of TP53 has been reported in 8-52% of SCLC tumors analyzed, which may be higher than in tumors in general (35%)[93]. TP53 alteration has been reported to be important for SCLC carcinogenesis[64]. The effect of TP53 alterations on prognosis in patients with SCLC has not been an area of significant focus in the literature (PubMed, Jun 2019).

### FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[94]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[95-97]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[98-100], including sarcomas[101-102]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[103] to 1:20,000[102]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[104]. In the appropriate clinical context, germline testing of TP53 is recommended.

# Atezolizumab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

## AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and patients with either PD-L1-positive or -negative urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, or PD-L1-positive triple-negative breast cancer. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

## SUPPORTING DATA

The Phase 3 IMpower133 trial reported that the addition of atezolizumab to carboplatin and etoposide as first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC) improved median OS (12.3 vs. 10.3, HR=0.70) and median PFS (5.2 vs. 4.3 months, HR=0.77) compared with the addition of placebo but did not improve ORR (60.2% vs. 64.4%) or median duration of response (4.2 vs 3.9 months)[107]. Those who had a blood-based TMB (bTMB) of ≥16 muts/Mb (n=80) and were treated with atezolizumab experienced a longer median OS (17.8 vs. 12.5 months) compared with patients with bTMB of <16 muts/Mb (n=271)[108]. The trial observed no survival benefit from added atezolizumab for a small subpopulation of patients with treated brain metastases and did not report any new safety signals[107]. A Phase 2 trial compared atezolizumab monotherapy with conventional chemotherapy for patients with relapsed SCLC and reported significantly shorter median PFS (1.4 vs. 4.3 months HR=2.26) and similar median OS (9.5 vs. 8.7 months, HR=0.84) with atezolizumab[109]. In a Phase 1a study of 17 heavily pretreated patients with ES-SCLC receiving atezolizumab as a monotherapy, median PFS was 1.5 months and median OS was 5.9 months, with the single PR lasting 7 months[110].

# Nivolumab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

## AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), and metastatic small cell lung cancer (SCLC). Furthermore, nivolumab is approved as both a single agent and in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

## SUPPORTING DATA

In multiple studies of SCLC, greater clinical benefit has been reported for the combination of nivolumab and ipilimumab compared with single-agent nivolumab. In the Phase 1/2 CheckMate-032 trial subgroup for patients with SCLC who progressed on platinum-based chemotherapy, nivolumab combined with ipilimumab elicited an ORR of 19–25% as compared with 10–11% with nivolumab alone, depending on the dosing strategy used[111-112]. The combination of nivolumab and ipilimumab also extended the median overall survival (mOS) to 7.9 months, compared with mOS of 4.1 months for nivolumab alone[111]. Similarly, in a preliminary report of a randomized expansion cohort of the same study, patients achieved better outcomes with the combination of nivolumab and ipilimumab compared with nivolumab alone (ORR of 21% vs. 12%, 12-week PFS rate of 30% vs. 18%)[111]. PD-L1 expression was not associated with clinical responses from nivolumab monotherapy or in combination with ipilimumab, or with TMB status[6,111]. A case report described a patient with SCLC transformation from EGFR-mutated lung adenocarcinoma who progressed on chemotherapy and did not benefit from subsequent treatment with single-agent nivolumab[113].

# Pembrolizumab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

## AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors, MSI-H or dMMR colorectal cancer (CRC) that has progressed on specific therapies, or PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma, cervical cancer, gastric cancer, esophageal cancer, or gastroesophageal junction (GEJ) carcinoma. It is also approved in various treatment settings for patients with melanoma, NSCLC, small cell lung cancer, HNSCC, urothelial carcinoma, hepatocellular carcinoma, or Merkel cell carcinoma. Combination treatments with pembrolizumab are approved for patients with NSCLC, renal cell carcinoma, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

## SUPPORTING DATA

A pooled analysis of the KEYNOTE-028 and KEYNOTE-158 trials, which investigated pembrolizumab for the treatment of advanced SCLC, reported an ORR of 19.3% (16/83), median PFS of 2.0 months, and median OS of 7.7 months for patients with at least 2 lines of prior therapy; 56.3% (9/16) of responders exhibited responses lasting 18 months or greater and 87.5% (14/16) of responders were PD-L1-positive[114-116] . Pembrolizumab combined with paclitaxel achieved an ORR of 23.1% (5/26 PRs, 1/26 CR), median PFS of 5.0 months, and median OS of 9.2 months for patients with refractory extensive-stage SCLC[117]. As maintenance therapy for extensive-stage SCLC after platinum/etoposide treatment, pembrolizumab did not prolong median PFS compared with historical data, although the observed 1-year PFS and OS rates (13% and 37%, respectively) suggest that some patients benefited[118].

## Avelumab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

### AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

### SUPPORTING DATA

Clinical data on the efficacy of avelumab for the treatment of lung small cell carcinoma are limited (PubMed, Jan 2020). The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[119], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[120], urothelial carcinoma[121], mesothelioma[111], ovarian carcinoma[122], and breast cancer[123], and from avelumab combined with axitinib in renal cell carcinoma[124]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[119,122-123] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[125-127] .

## Cemiplimab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

### AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

### GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

### SUPPORTING DATA

Cemiplimab has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[128]. Clinical responses have also been reported in non-small cell lung cancer (40% ORR, 1 CR and 7 PRs) and basal cell carcinoma (1 PR)[129-130] .

## Durvalumab

*Assay findings association*

***Tumor Mutational Burden***
18 Muts/Mb

### AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with urothelial carcinoma and non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data[5-7,105-106] , patients with SCLC whose tumors harbor a tumor mutational burden (TMB) of 13 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

### SUPPORTING DATA

Durvalumab achieved an ORR of 9.5% (2/21 PRs), a median PFS of 1.5 months, and a median OS of 4.8 months for patients with previously treated extensive-stage small cell lung cancer (SCLC) in a Phase 1/2 study[131]. In the first-line setting for patients with extensive-stage SCLC, the addition of durvalumab to etoposide and either cisplatin or carboplatin significantly improved median OS (13.0 vs. 10.3 months, HR=0.73)[132]. In combination with the anti-CTLA-4 antibody tremelimumab, the ORR was 13.3% (2/30 CRs, 2/30 PRs), the median PFS was 1.8 months, the median OS was 7.9 months, the 1-year OS rate was 41.7%, and the safety profile of the combination was deemed tolerable[133]. The combination of durvalumab and the PARP inhibitor olaparib has been evaluated in 2 Phase 2 studies and failed to reach the primary efficacy endpoints[134-135] .

**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.

**BIOMARKER**

## Tumor Mutational Burden

**RESULT**

18 Muts/Mb

**RATIONALE**

Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

### NCT03703297

**PHASE 3**

Study of Durvalumab + Tremelimumab, Durvalumab, and Placebo in Limited Stage Small-Cell Lung Cancer in Patients Who Have Not Progressed Following Concurrent Chemoradiation Therapy

**TARGETS**
PD-L1, CTLA-4

**LOCATIONS:** Edmonton (Canada), Arizona, California, Connecticut, Florida, Georgia, Illinois, Indiana, Kentucky, Winnipeg (Canada), Maryland, Massachusetts, Michigan, Minnesota, Montana, New Jersey, New York, North Carolina, North Dakota, Hamilton (Canada), London (Canada), Ottawa (Canada), Toronto (Canada), Oregon, Montreal (Canada), South Dakota, Tennessee, Texas, Washington, West Virginia, Caba (Argentina), Ciudadela (Argentina), Córdoba (Argentina), Mar del Plata (Argentina), Rosario (Argentina), San Salvador de Jujuy (Argentina), Aalst (Belgium), Brussels (Belgium), Bruxelles (Belgium), Hasselt (Belgium), Roeselare (Belgium), Brno (Czechia), Olomouc (Czechia), Ostrava (Czechia), Praha (Czechia), Praha 2 (Czechia), Berlin (Germany), Freiburg (Germany), Gauting (Germany), Gerlingen (Germany), Heidelberg (Germany), Köln (Germany), Mainz (Germany), Münster (Germany), Oldenburg (Germany), Regensburg (Germany), Wuerzburg (Germany), Bangalore (India), Bengaluru (India), Chennai (India), Gurgaon (India), Hyderabad (India), Karamsad (India), New Delhi (India), Vadodara (India), Milano (Italy), Orbassano (Italy), Roma (Italy), Rozzano (Italy), Terni (Italy), Bunkyo-ku (Japan), Chuo-ku (Japan), Fukuoka-shi (Japan), Iwakuni-shi (Japan), Kashiwa (Japan), Koto-ku (Japan), Kurume-shi (Japan), Nagoya-shi (Japan), Niigata-shi (Japan), Osakasayama (Japan), Sakai-shi (Japan), Sapporo-shi (Japan), Sendai-shi (Japan), Sunto-gun (Japan), Tokushima-shi (Japan), Ube-shi (Japan), Changwon-si (Korea, Republic of), Cheongju-si (Korea, Republic of), Daegu (Korea, Republic of), Goyang-si (Korea, Republic of), Gyeongsangnam-do (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Suwon-si (Korea, Republic of), Almelo (Netherlands), Amsterdam (Netherlands), Den Bosch (Netherlands), Groningen (Netherlands), Harderwijk (Netherlands), Kazan (Russian Federation), Kirov (Russian Federation), Moscow (Russian Federation), Obninsk (Russian Federation), Omsk (Russian Federation), Ufa (Russian Federation), Volgograd (Russian Federation), Barcelona (Spain), Madrid (Spain), Oviedo (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Kaohsiung City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Edirne (Turkey), Istanbul (Turkey), Izmir (Turkey), Konya (Turkey), Samsun (Turkey), Hanoi (Vietnam), Ho Chi Minh (Vietnam)

### NCT03059823

**PHASE 1**

A Phase 1 Study of MGA012 in Patients With Advanced Solid Tumors

**TARGETS**
PD-1

**LOCATIONS:** Arizona, Michigan, New Jersey, Darlinghurst (Australia), North Carolina, Texas, Virginia, Camperdown (Australia), Leuven (Belgium), Burgas (Bulgaria), Sofia (Bulgaria), Berlin (Germany), Munich (Germany), Gdynia (Poland), Kraków (Poland), Lublin (Poland), Otwock (Poland), Poznań (Poland), Warsaw (Poland), Barcelona (Spain), Madrid (Spain), Dniprodzerzhyns'k (Ukraine), Ivano-Frankivs'k (Ukraine), Sumy (Ukraine), Úzhgorod (Ukraine), London (United Kingdom), Sutton (United Kingdom)

### NCT04028050

**PHASE 3**

A Study of Atezolizumab in Combination With Carboplatin Plus Etoposide to Investigate Safety and Efficacy in Patients With Untreated Extensive-Stage Small Cell Lung Cancer

**TARGETS**
PD-L1, TOP2

**LOCATIONS:** Rionero In Vulture (PZ) (Italy), Avellino (Italy), Napoli (Italy), Bologna (Italy), Meldola (Italy), Aviano (Italy), Roma (Italy), Genova (Italy), Brescia (Italy), Milano (Italy), Ancona (Italy), Novara (Italy), Lecce (Italy), Sassari (Italy), Palermo (Italy), Taormina (Italy), Pisa (Italy), Treviso (Italy), Verona (Italy)

## NCT02734004

**PHASE 1/2**

A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors.

**TARGETS**
PARP, PD-L1, VEGFA

**LOCATIONS:** Georgia, Maryland, Massachusetts, Michigan, Missouri, Ohio, Pennsylvania, Bordeaux (France), Caen Cedex 05 (France), Clermont Ferrand cedex 01 (France), Dijon cedex (France), Marseille CEDEX 5 (France), Nantes (France), Paris cedex 14 (France), Pierre Benit Cedex (France), Villejuif Cedex (France), Haifa (Israel), Jerusalem (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Goyang-si (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Amsterdam (Netherlands), Maastricht (Netherlands), Nijmegen (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Chur (Switzerland), Lausanne (Switzerland), Cambridge (United Kingdom), Dundee (United Kingdom), Glasgow (United Kingdom), Greater London (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Sutton (United Kingdom)

## NCT03104699

**PHASE 1/2**

Phase 1 / 2 Study of AGEN2034 in Advanced Tumors and Cervical Cancer

**TARGETS**
PD-1

**LOCATIONS:** Antofagasta (Chile), Temuco (Chile), Arizona, California, Florida, Illinois, Kaunas (Lithuania), Kraków (Poland), Campbelltown (Australia), Randwick (Australia), Recife (Brazil), Gdynia (Poland), Benowa (Australia), Rio De Janeiro (Brazil), Santiago (Chile), Ijui (Brazil), Porto Alegre (Brazil), São Paulo (Brazil), North Adelaide (Australia), Texas, Vilnius (Lithuania), Brighton (Australia), Poznań (Poland), Washington, Brussels (Belgium), Charleroi (Belgium), Leuven (Belgium), Namur (Belgium), Sao Jose do Rio Preto (Brazil), Tallinn (Estonia), Bordeaux (France), Lyon (France), Marseille (France), Marseille Cedex 9 (France), Nice cedex 2 (France), Paris (France), Plérin (France), Saint-Herblain (France), Toulouse (France), Villejuif Cedex (France), Chisinau (Moldova, Republic of), Bydgoszcz (Poland), Warszawa (Poland), Barcelona (Spain), Pamplona (Spain), Valencia (Spain)

## NCT02628067

**PHASE 2**

Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/ KEYNOTE-158)

**TARGETS**
PD-1

**LOCATIONS:** California, Colorado, Florida, Georgia, Maryland, Massachusetts, New Jersey, Kirkland (Canada), Texas, North Ryde (Australia), Sao Paulo (Brazil), Bogota (Colombia), Glostrup (Denmark), Paris (France), Haar (Germany), Hod Hasharon (Israel), Rome (Italy), Chiyoda-Ku, Tokyo (Japan), Seoul (Korea, Republic of), Mexico City (Mexico), Haarlem (Netherlands), Drammen (Norway), Makati (Philippines), Moscow (Russian Federation), Midrand (South Africa), Madrid (Spain), Taipei (Taiwan), Hoddesdon (United Kingdom)

## NCT02829723

**PHASE 1/2**

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

**TARGETS**
PD-1, CSF1R

**LOCATIONS:** Nagoya (Japan), Hospitalet de LLobregat (Spain), Rozzano (Italy), Tennessee, Texas, Tel Aviv (Israel), Singapore (Singapore), Taipei (Taiwan)

## NCT02671435

**PHASE 1/2**

A Study of Durvalumab (MEDI4736) and Monalizumab in Solid Tumors

**TARGETS**
PD-L1, NKG2A

**LOCATIONS:** Arizona, Vancouver (Canada), California, Colorado, Florida, Illinois, Maryland, Massachusetts, Michigan, New Jersey, New York, Toronto (Canada), Pennsylvania, Rhode Island, Tennessee, Texas, Utah, Blacktown (Australia), Clayton (Australia), Waratah (Australia), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Leuven (Belgium), Quebec (Canada), Marseille CEDEX 5 (France), Nantes CEDEX 1 (France), Debrecen (Hungary), Milano (Italy), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Grafton (New Zealand), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Sutton (United Kingdom)

## NCT03459222

**PHASE 1/2**

An Investigational Study of Immunotherapy Combinations in Participants With Solid Cancers That Are Advanced or Have Spread

**TARGETS**
CTLA-4, PD-1, LAG-3

**LOCATIONS:** California, Colorado, Maryland, Missouri, North Sydney (Australia), Tennessee, Nedlands (Australia), Marseille Cedex 5 (France), Toulouse (France), Villejuif (France), Forli (Italy), Napoli (Italy), Barcelona (Spain), Madrid (Spain), Pamplona (Spain), Lausanne (Switzerland), Zurich (Switzerland), Newcastle Upon Tyne (United Kingdom), Oxford (United Kingdom)

CLINICAL TRIALS

## NCT03400332

**PHASE 1/2**

An Investigational Immuno-Therapy Study of Experimental Medication BMS-986253 Given in Combination With Nivolumab in Patients With Advanced Cancers

**TARGETS**
IL-8, PD-1

**LOCATIONS:** Edmonton (Canada), Vancouver (Canada), Colorado, Manchester (United Kingdom), Maryland, Nevada, New Jersey, New York, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Virginia, Birmingham (United Kingdom), Bruxelles (Belgium), Gent (Belgium), Napoli (Italy), Rozzano MI (Italy), Madrid (Spain), Malaga (Spain), Pamplona (Spain), Santiago Compostela (Spain), Lausanne (Switzerland), St.Gallen (Switzerland), Zuerich (Switzerland)

CLINICAL TRIALS

**GENE**
***RB1***

**ALTERATION**
K810*

**RATIONALE**
On the basis of preclinical evidence, RB1 loss or inactivation may predict sensitivity to Aurora kinase A inhibitors.

## NCT02719691

**PHASE 1**

Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

**TARGETS**
Aurora kinase A, mTORC1, mTORC2

**LOCATIONS:** Colorado

**NOTE** One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

***BRIP1***
P23A

***FGF19***
R140H

***KMT2A (MLL)***
R876T

***MLL2***
V4545F

***NOTCH2***
T2111A

***PIK3C2G***
D1033Y

***PTCH1***
E340Q

***SDHA***
amplification

***SETD2***
V1327L

***VHL***
E42Q

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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