FOUNDATIONONE®

Tumor Type
Lung adenocarcinoma

Date of Birth	DD.MM.YYYY	**Medical Facility**	Institut fuer Pathologie und Molekularpathologie		
Sex	XXXXX	**Ordering Physician**	Pathologie USZ	**Specimen Received**	DD.MM.YYYY
FMI Case #	XXXXXXXXXX	**Additional Recipient**	Not Given	**Specimen Site**	Lung
Medical Record #		**Medical Facility ID #**	XXXXXXX	**Date of Collection**	Not Given
Specimen ID	XXXXXXXXXXX	**Pathologist**	Not Given	**Specimen Type**	FFPE

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

9 genomic findings

4 therapies associated with potential clinical benefit

0 therapies associated with lack of response

20 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

KRAS G12C
CDKN2A p16INK4a deletion exon 1
DNMT3A A574fs*77
GNAS R189M
KEAP1 R260Q
SLIT2 E730*
TP53 E343*

Additional Findings†

Microsatellite status MS-Stable

Tumor Mutational Burden TMB-Intermediate; 18 Muts/Mb

Additional Disease-relevant Genes with No Reportable Alterations Identified†

EGFR
ALK
BRAF
MET
RET
ERBB2
ROS1

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

INFORMATION REGARDING PHARMACEUTICAL PRODUCTS AND CLINICAL TRIALS

Genomic Findings Detected	Swissmedic-Approved Therapies (in patient's tumor type)	Swissmedic-Approved Therapies (in another tumor type)	Potential Clinical Trials
Tumor Mutational Burden TMB-Intermediate; 18 Muts/Mb	Atezolizumab Nivolumab Pembrolizumab	Avelumab	Yes, see clinical trials section
KRAS G12C	None	None	Yes, see clinical trials section

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Genomic Findings Detected	Swissmedic-Approved Therapies (in patient's tumor type)	Swissmedic-Approved Therapies (in another tumor type)	Potential Clinical Trials
CDKN2A p16INK4a deletion exon 1	None	None	None
DNMT3A A574fs*77	None	None	None
GNAS R189M	None	None	None
KEAP1 R260Q	None	None	None
Microsatellite status MS-Stable	None	None	None
SLIT2 E730*	None	None	None
TP53 E343*	None	None	None

IMPORTANT: Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities); however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report includes scientific information. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies and clinical trials contained in this report, should not be used as the single basis for the therapy decision. The report should only be regarded and used as a supplementing source of information: All treatment decisions remain the full and final responsibility of the respective treating physician. For various reasons further explained below, both the therapies and the clinical trials listed in this report may not be complete and exhaustive. Please find the entire Swiss Prescribing Information on www.swissmedicinfo.ch.

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GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● ***Tumor Mutational Burden*** TMB-Intermediate; 18 Muts/Mb	**Gene and Alteration:** Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[1,2] and cigarette smoke in lung cancer[3,4], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[5,6,7,8,9], and microsatellite instability (MSI)[5,8,9]. The tumor seen here harbors an intermediate TMB. This level of TMB is high enough that it may be associated with sensitivity to immune checkpoint inhibitors in some tumor types, including anti-PD-1 therapy in non-small cell lung cancer[4], anti-PD-L1 therapy in bladder cancer[10], and anti-CTLA-4 therapy in melanoma[11], potentially due to expression of immune-reactive neo-antigens in these tumors[4]. However, in other studies of checkpoint inhibitors, including anti-PD-1 therapy in colorectal cancer[12], patients with tumors harboring intermediate TMB levels experienced lower rates of clinical benefit than those with high TMB. **Frequency and Prognosis:** Intermediate TMB has been reported in 30-31% of non-small cell lung carcinomas (NSCLC), including 30% of adenocarcinomas and 41% of squamous cell carcinomas (SCC) (Spigel et al., 2016; ASCO Abstract 9017). Intermediate TMB was frequently observed in NSCLC with BRAF (31%) or KRAS (39%) mutation (Spigel et al., 2016; ASCO Abstract 9017). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC (Schwartz et al., 2016; ASCO Abstract 8533)[13,14], several other large studies did find a strong association with increased TMB[15,16,17,18]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median overall survival (OS) for tumors with a higher number of mutations in a limited gene set compared with lower mutation number (48.4 vs. 61.0 months)[13]. **Potential Treatment Strategies:** On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[11], anti-PD-L1[10,19,20], and anti-PD-1 therapies[4,12,21]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[4]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab[4,12,21]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[22] or nivolumab[23], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[24], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[25]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[11,26] and anti-PD-1/anti-PD-L1 treatments[19]. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (muts) per megabase (Mb)] compared to nonresponders (6.4 muts/Mb)[10], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival[20].

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GENE ALTERATION	INTERPRETATION
KRAS G12C	**Gene and Alteration:** KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[27,28]. The KRAS gene is one of the most commonly mutated genes in human malignancies[29,30,31]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, A18D, L19F, D33E, G60_A66dup/E62_A66dup, and K117N have been characterized to be activating and oncogenic[27,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51]. **Frequency and Prognosis:** In the TCGA datasets, KRAS mutation was observed in 33% of lung adenocarcinoma cases[52] and in 1% of lung squamous cell carcinoma (SCC) cases[53]; amplification of KRAS was observed in 2.6% of lung adenocarcinomas[52] and 2.2% of lung SCCs[53]. Other studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 32-35% of lung adenocarcinomas (32-35%)[54,55,56,57,58,59,60,61,62], 10.5-33% of lung adenosquamous carcinomas[63,64,65], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[66]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior[56,62,67]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[68]. KRAS amplification associated with increased invasiveness of lung adenocarcinomas in one study[69]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[21].

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GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: While preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, including trametinib and cobimetinib[27,70,71,72,73,74], multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[75,76,77]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the progression-free survival (PFS) or overall survival of patients with KRAS-mutant NSCLC relative to docetaxel alone (Janne et al., 2016; ESMO Abstract LBA47_PR). In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[78]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[79,80,81], in spite of preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[82,83], RAF[84], pan-ERBB[85], or BCL2[86,87]. However, a Phase 1 combination trial of the MEK inhibitor PD-0325901 with the CDK4/6 inhibitor palbociclib that included 17 patients with KRAS-mutant NSCLC reported 1 partial response (PR), >50% stable disease, and 5 patients with PFS >6 months in this cohort; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among those with tumors harboring KRAS mutation and STK11 inactivation (Shapiro et al., 2017; AACR Abstract CT046). In addition to a PR in a patient with KRAS-mutant NSCLC, a Phase 1 trial evaluating the CDK4/6 inhibitor abemaciclib reported improved disease control rate (55% vs. 39%) and median PFS (2.8 vs. 1.9 months) for patients with KRAS-mutant NSCLC relative to those with KRAS wild-type NSCLC[88]. The reovirus Reolysin targets cells with activated RAS signaling[89,90,91] and is in clinical trials in some tumor types. A trial of Reolysin in combination with paclitaxel and carboplatin in patients with NSCLC harboring activating KRAS or EGFR alterations reported significantly improved response and survival rates compared to assumed historical data for paclitaxel and carboplatin alone[92]. A study of immune checkpoint inhibitors for patients with KRAS-mutant lung adenocarcinoma reported a reduced number of objective responses when comparing tumors with co-occurring STK11 mutation (0/6), TP53 mutation (3/12), or STK11/TP53 wild type (9/17) (Skoulidis et al., 2016; WCLC Abstract MA04.07). Although some studies have suggested that KRAS mutation status may predict lack of response to the EGFR inhibitors erlotinib and gefitinib in patients with lung cancer, a retrospective study suggests that there is no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wild-type and -mutant patients[93,94,95,96].
● ***CDKN2A*** p16INK4a deletion exon 1	**Gene and Alteration:** CDKN2A encodes two distinct tumor suppressor proteins, p16INK4a and p14ARF[97,98]. p16INK4a inhibits CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; inactivation of p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and cell cycle control[99,100]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via MDM2 inhibition[101,102]. This alteration is predicted to result in p16INK4a loss of function[103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123]; this alteration is not expected to affect the function of p14ARF[106,107]. **Frequency and Prognosis:** In the TCGA dataset, putative homozygous deletion of CDKN2A has been reported in 19% of lung adenocarcinoma samples analyzed, while CDKN2A mutation has been reported in 4% of cases[52]. 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 21-43% of NSCLC samples[99,124,125,126,127]. CDKN2A mRNA loss has been reported in 59% of NSCLC samples[128]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[124,129,130,131].

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GENE ALTERATION	INTERPRETATION
	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[132,133,134,135]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[136,137], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents (Gopalan et al., 2014; ASCO Abstract 8077, Peguero et al., 2016; ASCO Abstract 2528, Konecny et al., 2016; ASCO Abstract 5557)[138,139,140,141]; it is not known whether CDK4/6 inhibitors would be beneficial in this case.
● ***DNMT3A*** A574fs*77	**Gene and Alteration:** The DNMT3A gene encodes DNA methyltransferase 3A, an enzyme involved in the methylation of newly synthesized DNA, a function critical for gene regulation[142,143]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[144,145,146,147,148,149]. Both activating alterations (R771L)[150] and inactivating alterations due to the loss or disruption of the C-terminal catalytic domain (aa 627-912) or mutation of R882 have been identified[150,151,152,153,154]. Mutation of R882 has been shown to reduce methyltransferase activity in vitro and increase cell proliferation[150,153,154]. **Frequency and Prognosis:** DNMT3A mutations have been reported in 13.8% of hematopoietic and lymphoid malignancies and at lower frequencies in solid tumors, including those of the peritoneum (4.8%), skin (2.7%), large intestine (2.5%), small intestine (2.0%), and endometrium (1.7%) (COSMIC, 2017). DNMT3A mutations have been correlated with poor prognosis in acute myeloid leukemia (AML)[153,155,156], and associated with clonal hematopoiesis of indeterminate potential (CHIP) in hematologic malignancies[157,158,159,160,161]; however, the role of DNMT3A alterations in solid tumors is unclear. **Potential Treatment Strategies:** Emerging clinical evidence in AML and myelodysplastic syndrome (MDS) suggests that patients harboring DNMT3A mutations may benefit from DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine[154,162,163,164], and these are under investigation in clinical trials for solid tumors. Although DNMT inhibitors have been reported to be effective in the case of mutations at R882, there is no evidence to suggest that they are relevant in the case of other DNMT3A inactivating mutations or DNMT3A loss.
● ***GNAS*** R189M	**Gene and Alteration:** GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)[165]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase[165]. GNAS has been reported to be amplified in cancer[166] and may be biologically relevant in this context[167,168]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration[169,170,171,172,173,174] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations[175,176,177].

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GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[178,179] and appendiceal mucinous neoplasms (50-72%)[180,181] as well as in tumors affecting pituitary gland (27%), bone (15%), and pancreas (15%) (COSMIC, 2017). Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[182,183,184], colorectal adenocarcinoma (9%)[8], stomach adenocarcinoma (7%)[185], lung adenocarcinoma (6.5%)[52], breast invasive carcinoma (6.5%)[186], pancreatic adenocarcinoma (6%)[187], and sarcomas (5.8%)[188]. GNAS mutations are rare in hematological malignancies generally[189,190](COSMIC, 2017). Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome[191]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer[183,184], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer[192]. **Potential Treatment Strategies:** There are no therapies targeted to GNAS mutation in cancer.
● ***KEAP1*** R260Q	**Gene and Alteration:** KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate-specificity for a CUL3-dependent ubiquitin ligase[193]. This regulation is affected through suppression of NRF2, a transcription factor encoded by NFE2L2[194,195,196]. Inactivation of KEAP1 is hypothesized to promote tumor survival through constitutive activation of cytoprotective proteins normally regulated as part of the oxidative stress response. This hypothesis is strengthened by the observation that many tumors lacking KEAP1 mutations instead exhibit NFE2L2 mutations which prevent NRF2 recognition, and therefore polyubiquitination, by KEAP1/CUL3 E3 ligase[197]. KEAP1 mutations may be hypomorphic with respect to activating NRF2 but have been associated with DPP3 overexpression, which can result in a more complete activation of NRF2[196]. **Frequency and Prognosis:** Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[198]. NRF2 activation has been associated with poor prognosis in head and neck squamous cell carcinomas (HNSCC)[199]. **Potential Treatment Strategies:** There are no targeted therapies available to address inactivating mutations of KEAP1; however, loss of KEAP1 function may stabilize NRF2 and a number of compounds that inhibit NRF2 are being evaluated preclinically[200]. Additionally, KEAP1 mutation has been identified as a potential biomarker for sensitivity to combined AKT- and TXNRD1-inhibition in lung cancer[201].
● ***Microsatellite status*** MS-Stable	**Gene and Alteration:** 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[202]. 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[202,203,204]. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[205,206,207]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[202,204,206,207]. **Frequency and Prognosis:** MSI-high (MSI-H) has been reported at various frequencies in non-small cell lung cancer (NSCLC) as well as in small cell lung cancer[208,209,210,211,212,213]. One study observed MSI-H in 0.8% (4/480) of lung adenocarcinoma cases; the MSI-H tumors occurred in patients with smoking history, and 3/4 MSI-H cases had nonsynchronous carcinomas in other organs, although none of the patients were diagnosed with Lynch syndrome[208].

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GENE ALTERATION	INTERPRETATION
	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[214,215,216], including approved therapies nivolumab and pembrolizumab (Overman et al., 2016; ASCO Abstract 3501)[12]. 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) (Ayers et al., ASCO-SITC 2016; Abstract P60). Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)[12]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without (Overman et al., 2016; ASCO Abstract 3501).
● ***SLIT2*** E730*	**Gene and Alteration:** SLIT2 encodes a secreted glycoprotein which binds receptors of the ROBO family, and provides guidance for cell migration, particularly during development of the nervous system, by mediating repulsive cues. SLIT2, along with other components of the SLIT/ROBO pathway, has been reported to act as a tumor suppressor by suppressing cancer cell invasion[217]. **Frequency and Prognosis:** Mutations of SLIT2, or repression of SLIT2 expression by promoter hypermethylation, have been reported in aggressive cancer types with poor prognosis, such as pancreatic ductal adenocarcinoma[218] and small cell lung carcinoma[219], as well as in lung, colorectal, prostate, and bladder cancers, and in acute lymphocytic leukemia[220]. **Potential Treatment Strategies:** There are no approved therapies to directly target genomic alterations in SLIT2.
● ***TP53*** E343*	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[221]. 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[222,223,224]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[225,226,227,228,229,230]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[231] to 1:20,000[230], and in the appropriate clinical context, germline testing of TP53 is recommended. **Frequency and Prognosis:** TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[52,53,126,232,233,234,235,236]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[237]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[21].

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GENE ALTERATION	INTERPRETATION
	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 AZD1775[238,239,240,241] or p53 gene therapy and immunotherapeutics such as SGT-53[242,243,244,245,246] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease 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[247]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). 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 two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[246]. 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[248]. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

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THERAPIES

SWISSMEDIC-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Atezolizumab	**Approved Indications:** Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is Swissmedic approved to treat patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) following prior chemotherapy. **Gene Association:** On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017)[4], patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutation burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling, such as atezolizumab. **Supporting Data:** The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated non-small cell lung carcinoma (NSCLC) reported a significant increase in median overall survival (OS; 13.8 vs. 9.6 months) and duration of response (DOR; 16.3 vs. 6.2 months), with similar benefit for patients with squamous or non-squamous histology [hazard ratio (HR) of 0.73 for either group]; clinical benefit was observed regardless of PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% compared with <1% (HR of 0.41 vs. 0.75)[249]. Similar results were reported in the Phase 2 POPLAR study (OS of 12.6 vs. 9.7 months; DOR, 18.6 vs. 7.2 months)(Smith et al., 2016; ASCO Abstract 9028)[250]. Patients on this study who continued on atezolizumab after experiencing progressive disease (PD) achieved responses in 11% of cases and a median OS of 11.1 months, compared with 8.3 months for patients switching to different treatment (Mazieres et al., 2016; ASCO Abstract 9032). In another study of atezolizumab in patients with NSCLC, an overall response rate (ORR) of 23% (12/53) and a median progression-free survival of 15 weeks were reported[251]. Atezolizumab achieved similar ORRs for patients with NSCLC who received no prior chemotherapy (24-29%), progressed on previous platinum therapy (17-19%), or had brain metastases or treated asymptomatic brain metastases (17%) (Wakelee et al., 2016; IASLC Abstract ORAL01.04, Spigel et al., 2015; ASCO Abstract 8028).
Nivolumab	**Approved Indications:** Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is Swissmedic approved to treat unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved to treat advanced non-small cell lung cancer (NSCLC) after prior chemotherapy, advanced renal cell carcinoma following antiangiogenic therapy, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after prior platinum-based therapy, non-resectable or metastatic urothelial carcinoma after prior platinum-based chemotherapy, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation and brentuximab vedotin treatment. Furthermore, nivolumab is approved to treat mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) after prior treatment with a combination of fluoropyrimidine and irinotecan or oxaliplatin. **Gene Association:** On the basis of emerging clinical data (Spigel et al., 2016; ASCO Abstract 9017)[4,252], patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutation burden (TMB) may show greater benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling, such as nivolumab.

Supporting Data: For patients with platinum-refractory non-squamous NSCLC, nivolumab improved median overall survival (OS; 12.2 vs. 9.4 months) and the objective response rate (ORR; 19% vs. 12%) compared with docetaxel; PD-L1 expression was associated with benefit from nivolumab in this study [OS hazard ration (HR) of 0.40-0.59][253]. As second-line therapy for advanced squamous NSCLC, nivolumab resulted in longer median OS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[254,255]. Real-world studies of nivolumab reported clinical benefit for 35-36% of patients (Crino et al., 2016; ASCO Abstract 3067, Corny et al., 2016; ASCO Abstract e20633). First-line nivolumab for patients with advanced NSCLC and at least 5% PD-L1 expression did not improve progression-free survival (PFS) compared with investigator's choice of platinum-based doublet chemotherapy (PT-DC) (median PFS of 4.2 vs. 5.9 months, HR of 1.15); the median OS was 14.4 months with nivolumab compared to 13.2 months with chemotherapy (HR of 1.02)[252]. Exploratory subgroup analysis of tumor mutation burden (TMB), however, revealed that patients with elevated TMB (approximately 5 muts/Mb or more) experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)[252]. A Phase 1 study of first-line nivolumab alone or combined with ipilimumab every 6 or 12 weeks, respectively, reported ORRs of 23% (12/53), 38% (15/39) and 47% (18/38) and median PFS of 3.6, 3.9, and 8.1 months in unselected patients[256,257]; the 1-year OS rate with either ipilimumab combination was 87% for patients with at least 1% PD-L1 expression and 53% for those with less than 1% PD-L1 (Goldman et al., 2017; ASCO Abstract 9093). Combinations with PT-DC (gemcitabine/cisplatin, pemetrexed/cisplatin, and paclitaxel/carboplatin) resulted in ORRs of 33-47%, 1-year OS rates of 50-87%, and 2-year OS rates of 25-62%[258]. Nivolumab plus erlotinib for the treatment of chemotherapy-naive EGFR-mutant NSCLC achieved an ORR of 19%; additionally, 15% (3/20) partial responses (PRs) and 45% (9/20) stable diseases were reported in cases with acquired erlotinib resistance (Rizvi et al., 2014; ASCO Abstract 8022). Nivolumab has shown intracranial activity, with disease control in the brain for 33% of patients (Goldman et al., 2016; ASCO Abstract 9038)[259]. A study of 3 patients with resectable NSCLC reported 1 complete response and 1 PR with nivolumab as neoadjuvant therapy (Forde et al., 2016; ASCO Abstract e20005).

Pembrolizumab

Approved Indications: 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 Swissmedic approved to treat unresectable or metastatic melanoma, classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy, and advanced urothelial carcinoma after treatment with platinum-based chemotherapy. Pembrolizumab is also approved as first-line treatment for metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (at least 50% tumor proportion score) and without EGFR or ALK genomic alterations as well as for the treatment of patients with PD-L1-positive (at least 1% tumor proportion score) metastatic NSCLC following prior therapy. In patients with metastatic NSCLC whose tumors harbor EGFR or ALK alterations, pembrolizumab is available following prior treatments approved for these alterations.

Gene Association: On the basis of emerging clinical data (Spigel et al., 2016; ASCO Abstract 9017)[4], patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutation burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling, such as pembrolizumab.

Supporting Data: As first-line therapy for patients with EGFR/ALK wild-type advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab significantly improved median progression-free survival (PFS; 10.3 vs. 6.0 months) and 6-month overall survival (OS; 80.2% vs. 72.4%) and increased the objective response rate (ORR; 44.8% vs. 27.8%) compared with investigator's choice platinum-based chemotherapy[260]. First-line treatment of patients with EGFR/ALK wild-type advanced, nonsquamous NSCLC with pembrolizumab plus carboplatin and pemetrexed increased the ORR [55% (33/60) vs. 29% (18/63)] and PFS (13.0 vs. 8.9 months) compared with carboplatin and pemetrexed alone; 54% (21/39) of patients with PD-L1 expression on at least 1% of tumor cells and 57% (12/21) of patients with less than 1% expression responded[261]. In the same setting, pembrolizumab plus carboplatin and paclitaxel resulted in a ORR of 52% (13/25) for patients with NSCLC of any histology (Gadgeel et al., 2016; ASCO Abstract 9016). In a Phase 2/3 study for previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells, pembrolizumab extended median OS (10.4-12.7 vs. 8.2 months) when compared with docetaxel[262]. A Phase 1 study of pembrolizumab in NSCLC reported an ORR of 19% and median OS of 10.6 months and 22.1 months for previously treated and treatment naive patients, respectively (Hui et al., 2016; ASCO Abstract 9026)[263]. In both studies, pembrolizumab demonstrated greater efficacy in patients with PD-L1 expression on at least 50% of tumor cells, with ORRs (29-45%)[262,263], median OS (14.9-17.3 months)[262], and median PFS (5.0-6.3 months)[262,263] being increased for these patient populations. In a Phase 2 study of pembrolizumab for advanced PD-L1-positive NSCLC with brain metastases, 33% (6/18) patients experienced brain metastases responses[264]. Studies combining pembrolizumab with the immunotherapy ipilimumab for patients with recurrent advanced NSCLC with at least 1 previous treatment reported an ORR of 24% with 40% (18/45) stable disease, and median PFS and OS of 6 and 17 months, respectively (Gubens et al., 2016; ASCO Abstract 9027). A Phase 1 study of pembrolizumab in combination with the 4-1BB agonist utomilumab for the treatment of advanced solid tumors reported 1 partial response out of 6 patients with NSCLC (Tolcher et al., 2016; ASCO Abstract 3002).

SWISSMEDIC-APPROVED THERAPIES IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Avelumab	**Approved Indications:** 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 Swissmedic approved to treat patients with metastatic Merkel cell carcinoma who have progressed following chemotherapy. **Gene Association:** On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017)[4], patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutation burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab. **Supporting Data:** In a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the overall response rate (ORR) was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median progression-free survival (PFS) was 12 weeks for both cohorts (Verschraegen et al., 2016; ASCO Abstract 9036)[265]. In patients with NSCLC and PD-L1-positive tumor cells, first-line treatment with avelumab resulted in numerically increased ORR (20%; 7/35 vs. 0%; 0/10) and a trend toward prolonged PFS (11.6 vs. 6.0 weeks) relative to patients with fewer than 1% of tumor cells expressing PD-L1 (Verschraegen et al., 2016; ASCO Abstract 9036); however, response rates, PFS, and OS were similar regardless of immune or tumor cell PD-L1 expression in patients who had previously received platinum-based treatment[265].

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Tumor Type
Lung adenocarcinoma

IMPORTANT: Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities), however the agents listed in this report may have little or no evidence in the patient's tumor type. In addition, the above list is not meant to be a complete and exhaustive list of available therapies. The therapies listed in this report are limited to pharmaceutical drug products and the therapies listed may not be a complete and exhaustive list of available pharmaceutical drug products. This report does not include medical devices, which may be approved for treatment in the particular patient indication. In addition, there may be therapies available which are neither a pharmaceutical product nor a medical device, e.g. rather a treatment method, surgical procedure or a cell therapy and similar methods which may not be subject to approval by the applicable regulatory authorities. There may be pharmaceutical products available which are not authorized by certain applicable regulatory authorities. The therapies approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities) in other tumor types listed in this report may not be complete and exhaustive because these may not be linked to a specific gene defect or because they were only authorized for other indications. The basis for the search of approved drugs may not be up-to date or may not be accurate. In addition, search errors when searching the therapies cannot be ruled out completely. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies contained in this report, should not be used as the single basis for the therapy decision. The description of the approved indication in this report is a summary and does not include the exact wording of the approved indication. It is the responsibility of the treating physicians to check the exact indication of any approved label/SmPC/prescribing information for any therapy available in the respective country.

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Tumor Type
Lung adenocarcinoma

CLINICAL TRIALS TO CONSIDER

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.

The clinical trials to consider listed in this report may not be complete and exhaustive or may include trials in which the patient cannot participate. Please keep in mind that the information available in the public domain is continually updated and should be investigated by the physician or research staff. There may also be compassionate use programs where patients could be included, and these programs are not listed in this report. The clinical trial information may not be up to date or may not be accurate. In addition, search errors when searching the clinical trials cannot be ruled out completely.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
Tumor Mutational Burden TMB-Intermediate; 18 Muts/Mb	Increased tumor mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "PD-L1", "B7-H1", "PD-1", "pembrolizumab", "nivolumab", "atezolizumab", "MPDL3280A", "durvalumab", "MEDI4736", "avelumab", "MSB0010718C", "BMS-936559", "pidilizumab", "CT-011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects With Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)	Phase 3	CTLA-4, PD-1	South Carolina, Majadahonda (Spain), Morelia (Mexico), Saxonwold, Johannesburg (South Africa), Barretos (Brazil), Hradec Kralove (Czechia), St. Petersburg (Russian Federation), Gera (Germany), Heraklio (Greece), Utah, Neo Faliro (Greece), Immenstadt (Germany), Chelyabinsk (Russian Federation), Johannesburg (South Africa), Marseille Cedex 20 (France), Yokohama-Shi (Japan), Pretoria (South Africa), Halle (Germany), Heidelberg (Germany), Wakayama-shi (Japan), Cheongju-si (Korea, Republic of), Hemer (Germany), Df (Mexico), Chiba-shi (Japan), Ciudad Autonoma De Buenos Aire (Argentina), Recoleta (Chile), Caen (France), Bad Berka (Germany), Rio De Janeiro (Brazil), Essen (Germany), Livorno (Italy), Sunto-gun (Japan), New Jersey, Basel (Switzerland), Fitzroy (Australia), Romania (Romania), Tamworth (Australia), Charleroi	NCT02477826

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Tumor Type
Lung adenocarcinoma

			(Belgium), Shinjuku-ku (Japan), Breda (Netherlands), Middlesborough (United Kingdom), Kobe-shi (Japan), Quebec (Canada), S.Andrea Fratte PG (Italy), Kentucky, Sint Niklaas (Belgium), Sapporo-shi (Japan), Budapest (Hungary), Nanchang (China), Athens (Greece), Okayama-shi (Japan), Monterrey (Mexico), Porto Alegre (Brazil), Rotterdam (Netherlands), Bogota (Colombia), Gliwice (Poland), Grosshansdorf (Germany), Cordoba (Argentina), Magdeburg (Germany), Gent (Belgium), Berlin (Germany), Medellin (Colombia), Vereeniging (South Africa), Kurashiki-shi (Japan), San Luis Potosi (Mexico), Oulu (Finland), Maryland, Turku (Finland), Wroclaw (Poland), Kanazawa-shi (Japan), Praha 4 (Czechia), Merida (Mexico), Wiesbaden (Germany), Bydgoszcz (Poland), Connecticut, Edmonton (Canada), Strasbourg (France), Valencia (Spain), San Miguel de Tucuman (Argentina), Vina Del Mar (Chile), Hiroshima-shi (Japan), Gdynia (Poland), Mexico (Mexico), Moscow (Russian Federation), Badalona (Barcelona) (Spain), North Carolina, Veldhoven (Netherlands), ANGERS Cedex 2 (France), Brisbane (Australia), Ijui (Brazil), Avellino (Italy), Jerusalem (Israel), Toulon (France), Ufa (Russian Federation), Olomouc (Czechia), Rimouski (Canada), Texas, Tao-yuan County (Taiwan), Leicester (United Kingdom), Akashi-shi (Japan), Floresti (Romania), Roma (Italy), Bunkyo-ku (Japan), Georgia, New York, Kashiwa-shi (Japan), Muenchen	

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Tumor Type
Lung adenocarcinoma

			(Germany), Hangzhou (China), Kitaadachi-gun (Japan), Birmingham (United Kingdom), Washington, Salvador (Brazil), Hirakata-shi (Japan), East Bentleigh (Australia), Edegem (Belgium), Haerbin (China), Milan (Italy), Sao Paulo (Brazil), Seoul (Korea, Republic of), Ravenna (Italy), Pennsylvania, Bergamo (Italy), Viedma (Argentina), Ciudad de Buenos Aires (Argentina), Pribram (Czechia), Frankfurt (Germany), Kurume-shi (Japan), Winterthur (Switzerland), Warszawa (Poland), Graz (Austria), Matsuyama-shi (Japan), Beirut (Lebanon), Guanzhou (China), Creteil (France), Perth (Australia), Bron (France), Takatsuki-shi (Japan), Fukuoka-shi (Japan), Pessac (France), Xi'an (China), Nagoya-shi (Japan), Limoges Cedex (France), Seongnam-si (Korea, Republic of), Murdoch (Australia), Shanghai (China), Tel-hashomer (Israel), Lodz (Poland), Chuo-ku (Japan), Toluca (Mexico), Trois-Rivieres (Canada), Rouen (France), Osaka-shi (Japan), Kazan (Russian Federation), Lausanne (Switzerland), Chur (Switzerland), Hasselt (Belgium), Sevilla (Spain), Surrey (United Kingdom), Tennessee, Zhengzhou (China), Santiago (Chile), Matrahaza (Hungary), Ota-shi (Japan), Dublin (Ireland), Galway (Ireland), Zerifin (Israel), Milano (Italy), Blacktown (Australia), London (United Kingdom), St. John's (Canada), Roeselare (Belgium), Cuautitlan Izcalli (Mexico), Bucharest (Romania), Montreal (Canada), Rennes Cedex 9 (France), Natori-shi (Japan), Vienna (Austria), Pereira	

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Tumor Type
Lung adenocarcinoma

			(Colombia), Bologna (Italy), Amsterdam (Netherlands), Madrid (Spain), Napoli (Italy), Alabama, Cambridgeshire (United Kingdom), Berazategui (Argentina), Saint Herblain (France), Dublin 8 (Ireland), Niigata-shi (Japan), Lima (Peru), Paris (France), Osakasayama-shi (Japan), Koto-ku (Japan), Chihuahua (Mexico), Gosford (Australia), London (Canada), Edinburgh (United Kingdom), Taichung (Taiwan), Limerick (Ireland), Craiova (Romania), Kfar-saba (Israel), Taipei (Taiwan), Terni (Italy), Yokohama-shi (Japan), Capital Federal (Argentina), Wels (Austria), California, Besancon Cedex (France), Southampton (United Kingdom), Messina (Italy), Petach Tikva (Israel), Missouri, Sherbrooke (Canada), Barcelona (Spain), Gdansk (Poland), Sendai-shi (Japan), Elizabeth Vale (Australia), Saint Priest En Jarez (France), Gerlingen (Germany), Saint-Petersburg (Russian Federation), Mar Del Plata (Argentina), Guadalajara (Mexico), Ohio, Thessaloniki (Greece), Garran (Australia)	
A Phase I/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors	Phase 1 / Phase 2	LAG-3, PD-1	Illinois, Essen (Germany), Helsinki (Finland), Zürich (Switzerland), Milano (Italy), Lausanne (Switzerland), Amsterdam (Netherlands), Maryland, Copenhagen (Denmark), London (United Kingdom), Toulouse Cedex 9 (France), Barcelona (Spain), Oslo (Norway), Wien (Austria), Michigan, Vlllejuif (France), Pennsylvania, Washington, Napoli (Italy), Herlev (Denmark), New York, ZB B rich (Switzerland), Pamplona (Spain), Massachusetts, Oregon	NCT01968109

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An Open-Label, Multicohort, Phase II Study of Atezolizumab in Advanced Solid Tumors	Phase 2	PD-L1	Southampton (United Kingdom), Rio de Janeiro (Brazil), Aarhus C (Denmark), Fribourg (Switzerland), Odense C (Denmark), Paris (France), Edirne (Turkey), Vancouver (Canada), Dublin (Ireland), Trier (Germany), Utrecht (Netherlands), Texas, Heidelberg (Germany), Hamburg (Germany), Wien (Austria), Napoli (Italy), Moscow (Russian Federation), Bebington (United Kingdom), Herlev (Denmark), Helsinki (Finland), Bordeaux (France), Graz (Austria), Saint-Petersburg (Russian Federation), Bydgoszcz (Poland), Warszawa (Poland), Istanbul (Turkey), New York, Barcelona (Spain), Lublin (Poland), Rotterdam (Netherlands), Villejuif (France), Porto Alegre (Brazil), Siena (Italy), Sao Paulo (Brazil), Milano (Italy), Pamplona (Spain), Amsterdam (Netherlands)	NCT02458638
A Phase III, Open-Label, Randomized Study of Atezolizumab (MPDL3280A, Anti-Pd-L1 Antibody) in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Patients Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer	Phase 3	PD-L1	Connecticut, Minnesota, Florida, Girona (Spain), Marseille (France), Malaga (Spain), Edegem (Belgium), Moscovskaya Oblast (Russian Federation), Maryland, Kentucky, Santiago (Chile), Kyiv (Ukraine), Breda (Netherlands), New York, Panevezys (Lithuania), Kaohsiung (Taiwan), Montpellier (France), Valencia (Spain), Holon (Israel), Oregon, Burgos (Spain), Kirovograd (Ukraine), Badalona (Spain), Buenos Aires (Argentina), Alicante (Spain), Constanta (Romania), Torokbalint (Hungary), Truro (United Kingdom), Roma (Italy), Parma (Italy), Lugo (Spain), Kepala Batas (Malaysia), Pamplona (Spain), Gyor (Hungary), Szombathely	NCT02657434

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Tumor Type
Lung adenocarcinoma

			(Hungary), Kaoshiung City (Taiwan), Darlinghurst (Australia), Washington, Bristol (United Kingdom), Yaroslavl (Russian Federation), Bucharest (Romania), EDE (Netherlands), Iasi (Romania), South Brisbane (Australia), Zaporizhzhya (Ukraine), London (United Kingdom), Cairns (Australia), Sittard-Geleen (Netherlands), Plymouth (United Kingdom), Sydney (Australia), Lima (Peru), Bucuresti (Romania), El Palmar (Spain), Hangzhou City (China), Inverness (United Kingdom), Harderwijk (Netherlands), Frankston (Australia), Lucca (Italy), Geelong (Australia), Farkasgyepu (Hungary), Lecce (Italy), Pennsylvania, Georgia, Limoges (France), Petah Tikva (Israel), Barcelona (Spain), Saint-Mande (France), Indiana, Oxford (United Kingdom), Dnipropetrovsk (Ukraine), Seoul (Korea, Republic of), Steyr (Austria), Sabadell (Spain), Cherkasy (Ukraine), Cluj-Napoca (Romania), Cardiff (United Kingdom), Donostia (Spain), Creteil (France), Matosinhos (Portugal), Viña del Mar (Chile), Elche (Spain), Preston (United Kingdom), Dalin, Chiayi (Taiwan), L'Hospitalet de Llobregat (Spain), Liuying Township (Taiwan), Salamanca (Spain), Bron (France), Kuala Lumpur (Malaysia), Senhora da Hora - Porto (Portugal), Redcliffe (Australia), California, Wels (Austria), Village Branipole (Bulgaria), North Carolina, Romford (United Kingdom), Dublin (Ireland), Sevilla (Spain), Maine, Hobart (Australia), Ballarat (Australia), Madrid (Spain), Riga (Latvia), New Jersey, Mulhouse (France),	

			Sumy (Ukraine), Toulon (France), Temuco (Chile), Taipei City (Taiwan), Taipei (Taiwan), Clermont-ferrand (France), La Curuna (Spain), Michigan, Texas, Loures (Portugal), Khmelnytskyi (Ukraine), Nebraska, Székesfehérvár (Hungary), Tilburg (Netherlands), Sofia (Bulgaria), Mataro (Spain), Viedma (Argentina), Ravenna (Italy), Pahang (Malaysia), Chelyabinsk (Russian Federation), Virginia, Illinois, Glasgow (United Kingdom), Wisconsin, Cordoba (Argentina), Avignon (France)	
A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received up to 12 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks	Phase 3	PD-1	St. Jerome (Canada), North Carolina, Louisiana, California, Angers (France), Las Palmas de Gran Canaria (Spain), Tennessee, Bedford Park (Australia), Montreal (Canada), Cergy-pontoise (France), Freiburg im Breisgau (Germany), South Dakota, Roma (Italy), Alabama, Nimes (France), Paris (France), Colorado, Kentucky, Westmead (Australia), Hobart (Australia), St. Leonards (Australia), Kiel (Germany), Moers (Germany), Mississippi, Newmarket (Canada), South Carolina, El Palmar (Spain), Maine, Villefranche-sur-Sa?ne (France), Florida, N?rnberg (Germany), Kansas, Vandoeuvre-les-Nancy (France), Adelaide (Australia), Wien (Austria), Arizona, Le Mans (France), Dresden (Germany), Monza (Italy), New York, Seville (Spain), Gauting (Germany), Leipzig (Germany), Washington, Hamburg (Germany), Virginia, Clermont-ferrand Cedex 01 (France), Tours (France), Maryland, Ohio, Texas, Hannover (Germany), Indiana, Berlin	NCT02713867

			(Germany), Minnesota, Woolloongabba (Australia), Georgia, Bayonne (France), Waratah (Australia), Michigan, Sabadell-Barcelona (Spain), Suresnes (France), Heidelberg (Australia), Bad Berka (Germany), Nebraska, Oregon, Quebec (Canada), Lostau (Germany), Elizabeth Vale (Australia), Missouri, Kassel (Germany), Villefranche-sur-SaB B ne (France), NB B rnberg (Germany), Greifenstein (Germany), Napoli (Italy), Murdoch (Australia), Illinois, Mulhouse (France), Lucca (Italy)	
A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer	Phase 3	PD-L1	Townsville (Australia), Cordoba (Spain), Arkansas, Changhua City (Taiwan), Barcelona (Spain), Etobicoke (Canada), Michigan, Pordenone (Italy), Immenhausen (Germany), Budapest (Hungary), Milano (Italy), Bochum (Germany), Saransk (Russian Federation), Novara (Italy), Poznan (Poland), Aichi (Japan), Tennessee, Coimbra (Portugal), Holon (Israel), Loewenstein (Germany), Koln (Germany), Volzhskiy (Russian Federation), Missouri, Heidelberg (Germany), Ramat Gan (Israel), Kumamoto (Japan), Woolloongabba (Australia), Birmingham (United Kingdom), Torokbalint (Hungary), 'S Hertogenbosch (Netherlands), Hokkaido (Japan), Wakayama (Japan), Hemer (Germany), Lugo (Spain), Iasi (Romania), Grimsby (United Kingdom), Kitakyushu-shi (Japan), St Petersburg (Russian Federation), Toulon (France), Mississippi, Taichung (Taiwan), Saitama (Japan), Shenyang (China), Orbassano (Italy), Florida, Saint Petersburg (Russian Federation), Verona	NCT02486718

FOUNDATIONONE

Tumor Type
Lung adenocarcinoma

			(Italy), Washington, Bruxelles (Belgium), Zaporizhzhya (Ukraine), Bielefeld (Germany), Saint-Petersburg (Russian Federation), Kyoto (Japan), Kentucky, Akashi (Japan), Connecticut, Miyagi (Japan), Otwock (Poland), Torino (Italy), Brescia (Italy), Frankfurt am Main (Germany), Bergamo (Italy), Niigata-shi (Japan), Ohio, Putzu (Taiwan), Szolnok (Hungary), Groningen (Netherlands), Mont De Marsan (France), Strasbourg (France), Shatin (Hong Kong), Halle (Germany), Oldenburg (Germany), Saint-Mande (France), Petach Tikva (Israel), Tokyo (Japan), Virginia, Pisa (Italy), Fukuoka (Japan), Lyon (France), S. Cristobal de la Laguna (Spain), Sumy (Ukraine), Kryvyi Rih (Ukraine), Pecs (Hungary), Malvern (Australia), Shizuoka (Japan), Roma (Italy), Texas, London (United Kingdom), Hiroshima (Japan), Vinnytsia (Ukraine), Liège (Belgium), Beer Yaakov (Israel), Suzhou (China), Oregon, Utrecht (Netherlands), Nizhny Novgorod (Russian Federation), Limoges (France), Braunschweig (Germany), Haifa (Israel), Kaohsiung City (Taiwan), Moscow (Russian Federation), East York (Canada), Rhode Island, Pennsylvania, Jeollanam-do (Korea, Republic of), Großhansdorf (Germany), Liuying Township (Taiwan), Bunkyo-ku (Japan), Colchester, Essex (United Kingdom), Iowa, Cuneo (Italy), Craiova (Romania), Uzhhorod (Ukraine), Matsuyama-shi (Japan), Kfar-Saba (Israel), Tel Aviv (Israel), Homburg/Saar (Germany), Rehovot (Israel), Laval (Canada), Taranto (Italy),	

			Amsterdam (Netherlands), Nebraska, Montpellier (France), Maine, Valencia (Spain), München (Germany), Kanagawa (Japan), Okayama (Japan), Nieuwegein (Netherlands), Dnipropetrovsk (Ukraine), Chieti (Italy), Nevada, Regensburg (Germany), Marseille (France), Arizona, Palermo (Italy), Kharkiv (Ukraine), Santander (Spain), Maryland, Hamburg (Germany), District of Columbia, Taipei City (Taiwan), Taipei (Taiwan), Berlin (Germany), California, Porto (Portugal), South Carolina, Nantes (France), Saint-Quentin (France), Changhua (Taiwan), New York, Madrid (Spain), New Jersey, Lisboa (Portugal), North Carolina, Saint Pierre (France), Georgia, Palma De Mallorca (Spain), Münster (Germany), Zaragoza (Spain), Illinois, Taoyuan City (Taiwan), Suwon-si, (Korea, Republic of), Eindhoven (Netherlands), Trento (Italy), Shanghai (China)	
A Phase II, Multicenter, Open-label Study of EGF816 in Combination With Nivolumab in Adult Patients With EGFR Mutated Non-small Cell Lung Cancer and of INC280 in Combination With Nivolumab in Adult Patients With cMet Positive Non-small Cell Lung Cancer	Phase 2	MET, EGFR, PD-1	Madrid (Spain), Camperdown (Australia), Singapore (Singapore), Adelaide (Australia), Wurzburg (Germany), Pisa (Italy), Alicante (Spain), Perugia (Italy), Koeln (Germany), Aviano (Italy), Caen Cedex (France), Chur (Switzerland), Texas, Chermside (Australia), Alabama, North Carolina, Malaga (Spain), Genève (Switzerland), La Tronche (France), Barcelona (Spain), Amsterdam (Netherlands)	NCT02323126
A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability and Efficacy of Anti-KIR (Lirilumab) Administered in Combination With Anti-PD-1 (Nivolumab) in Patients With Advanced Solid Tumors	Phase 1/Phase 2	CTLA-4, PD-1, KIR	NONE	NCT01714739

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A Phase 2, Fast Real Time Assessment of Combination Therapies in Immuno-Oncology Study in Subjects With Advanced Non-Small Cell Lung Cancer (FRACTION-Lung)	Phase 2	ABL, LAG-3, CTLA-4, PD-1, SRC, DDR2, KIT, PDGFRs	Milan (Italy), California, New York, Rozzano (Italy), Nevada, Washington, Maryland, Virginia, Milano (Italy), Texas, Tennessee, Missouri, Paris (France), Kansas, Villejuif (France), Oregon, Colorado, Connecticut, Villejuif Cedex (France), Madrid (Spain), Michigan, Edmonton (Canada), Ohio, Massachusetts, Utah, Pennsylvania, Ottawa (Canada), Clayton (Australia), Pamplona (Spain)	NCT02750514
Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	Phase 2	AKTs, FGFRs, EGFR, PD-L1, RET, ERBB2, SRC, mTORC1, ERBB3, MEK, VEGFRs, mTORC2	Chartres (France), Clermont-Ferrand (France), Villejuif (France), Dijon (France), Toulon (France), Caen (France), Bordeaux (France), Nantes (France), Grenoble (France), Pierre Bénite (France), Toulouse (France), Marseille (France), Lyon (France), Lille (France), Créteil (France), Paris (France), Tours (France), Avignon (France)	NCT02117167

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CLINICAL TRIALS TO CONSIDER

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***KRAS*** G12C	KRAS activating mutations may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Also, clinical evidence suggests that patients with KRAS-mutant non-small cell lung cancer (NSCLC) may be sensitive to the CDK4/6 inhibitor abemaciclib. However, KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "KRAS", "MEK", "reolysin", "trametinib", "cobimetinib", "MEK162", "PD-0325901", "lung adenocarcinoma", "NSCLC", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma	Phase 2	CDK4, CDK6	Lille Cedex (France), Kentucky, Saint-Brieuc (France), Toulouse cedex 9 (France), North Carolina, Madrid (Spain), Liege (Belgium), Newcastle (Australia), Hawaii, Sevilla (Spain), Ottawa (Canada), District of Columbia, Grafton (New Zealand), Michigan, Tennessee, Tel Aviv Jaffa (Israel), Pamplona (Spain), Lyon Cedex 08 (France), Charleroi (Belgium), Oregon, Nedlands (Australia), Missouri, Brussel (Belgium), California, Lille (France), Wien (Austria), Montreal (Canada), Paris Cedex 05 (France), Padova (Italy), Massachusetts, Southport (Australia), Colorado, Florida, Texas, Barcelona (Spain), Jerusalem (Israel), New York, Woolloongabba (Australia), Genova (Italy), Leuven (Belgium), Roma (Italy), New Mexico, Tel Hashomer (Israel)	NCT02308020
A Phase 1b Study of Abemaciclib in Combination With Pembrolizumab for Patients With Stage IV Non-Small Cell Lung Cancer or Hormone Receptor Positive, HER2 Negative Breast Cancer	Phase 1	CDK4, PD-1, CDK6	Lille (France), Michigan, Istanbul (Turkey), Taipei (Taiwan), Toulouse (France), Villejuif (France), Liege (Belgium), Edegem (Belgium), Caceres (Spain), Massachusetts, Milano (Italy), Avila (Spain), California, Jhonghe City (Taiwan), Madrid	NCT02779751

			(Spain), Izmir (Turkey), Colorado, Arkansas, New York, Meldola (Italy), Leuven (Belgium), Montpellier (France), Tainan (Taiwan), Neihu Taipei (Taiwan)	
Phase I/II Study With the Combination of Dacomitinib and PD-0325901 in Metastatic KRAS Mutation Positive Colorectal, Non-small Cell Lung and Pancreatic Cancer	Phase 1 / Phase 2	EGFR, TOP1, ERBB2, MEK, ERBB4	Rotterdam (Netherlands), Amsterdam (Netherlands), Utrecht (Netherlands)	NCT02039336
Phase I/II Study With Lapatinib Plus Trametinib in Patients With Metastatic KRAS Mutant Colorectal, Non-small Cell Lung and Pancreatic Cancer	Phase 1 / Phase 2	EGFR, ERBB2, MEK	Amsterdam (Netherlands)	NCT02230553
Phase I/II Study With the Combination of Afatinib and Selumetinib in Advanced KRAS Mutant Positive and PIK3CA Wildtype Colorectal, Non-small Cell Lung and Pancreatic Cancer	Phase 1 / Phase 2	EGFR, ERBB2, MEK, ERBB4	Amsterdam (Netherlands)	NCT02450656
A Phase Ib/IIa Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers	Phase 1 / Phase 2	mTORC1, MEK, mTORC2	London (United Kingdom)	NCT02583542
National Lung Matrix Trial: Multi-drug, Genetic Marker-directed, Non-comparative, Multi-centre, Multi-arm Phase II Trial in Non-small Cell Lung Cancer	Phase 2	AKTs, CDK4, FGFRs, EGFR, mTORC1, MEK, AXL, mTORC2, TRKC, TRKA, MET, ALK, PD-L1, ROS1, CDK6	Leeds (United Kingdom), Birmingham (United Kingdom), Cardiff (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Newcastle (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Edinburgh (United Kingdom)	NCT02664935
An Open Label, Phase Ib Dose-escalation Study Evaluating the Safety and Tolerability of BI 836845 and Abemaciclib in Patients With Locally Advanced or Metastatic Solid Tumors and in Combination With Endocrine Therapy in Patients With Locally Advanced or Metastatic Hormone Receptor-positive Breast Cancer, Followed by Expansion Cohorts	Phase 1	CDK4, Aromatase, ER, IGF-2, IGF-1, CDK6	Connecticut, Paris (France), Barcelona (Spain), Minnesota	NCT03099174
Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With CJM112, EGF816, Ilaris® (Canakinumab) or Mekinist® (Trametinib)	Phase 1	EGFR, interleukin-17A, PD-1, MEK, interleukin-1 beta	Texas, Tennessee, Hospitalet de LLobregat (Spain), Villejuif Cedex (France), Madrid (Spain), Montreal (Canada), Singapore (Singapore), Brussels (Belgium), Toronto (Canada)	NCT02900664
A Sequential Phase I Study of MEK1/2 Inhibitors PD-0325901 or Binimetinib Combined With cMET Inhibitor PF-02341066 in Patients With RAS Mutant and RAS Wild Type (With Aberrant c-MET) Colorectal Cancer	Phase 1	MET, ALK, ROS1, MEK, AXL, TRKC, TRKA	Oxford (United Kingdom)	NCT02510001

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VARIANTS OF UNKNOWN SIGNIFICANCE

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.

BARD1	***CCND2***	***CIC***	***DDR2***	***EMSY***	***FLT4***
A721T	R285Q	P1050L	P448T	S516R	K1032M
GLI1	***IKZF1***	***LRP1B***	***PALB2***	***PDK1***	***PIK3CG***
R648S	R408S	S3273Y	T214I	A339S, M156V	S1003G
PMS2	***PREX2***	***RB1***	***SPEN***	***STK11***	***ZNF217***
E422D	A1409E	G203W	G3464A	Y246D	D447Y

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GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all 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 315 genes as well as introns of 28 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	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection of Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

Additional Assays: For the Detection of Select Cancer Biomarkers

Microsatellite status
Tumor Mutational Burden

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FOUNDATIONONE PERFORMANCE SPECIFICATIONS

The median exon coverage of this sample is 891x.

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99.0% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Sensitivity: Microsatellite status	At ≥20% tumor nuclei	97.0% (CI* 89.6%-99.6%)
Specificity: all variant types	Positive Predictive Value (PPV)	>99.0%
Specificity: Microsatellite status	Positive Predictive Value (PPV)	>95.0%
Accuracy: Tumor Mutational Burden	At ≥20% tumor nuclei	>90.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision 95.8% microsatellite status precision 96.4% tumor mutational burden precision

*95% Confidence Interval

** Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

[1] Based on analysis of coverage and rearrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.

[2] Based on ALK rearrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. et al. Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

Based on analytic validation of ROS1 gene coverage in the FoundationOne assay, the sensitivity of ROS1 rearrangement detection is estimated to be approximately 90%.

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

Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne test. Microsatellite status is assayed for all FoundationOne samples and may be reported as “MSI-High”, “MSI-Intermediate”, “MS-Stable”, or “Cannot Be Determined”. Microsatellite status is reported as “Cannot Be Determined” if the sample is not of sufficient quality to be confidently determined.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne and FoundationOne Heme tests and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne and FoundationOne Heme samples and may be reported as “TMB-High”, “TMB-Intermediate”, “TMB-Low”, or “Cannot Be Determined”. TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to fewer than or equal to 5 Muts/Mb. Tumor Mutational Burden is reported as “Cannot Be Determined” if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

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Tumor Type
Lung adenocarcinoma

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FOUNDATIONONE®

Tumor Type
Lung adenocarcinoma

APPENDIX

ABOUT FOUNDATIONONE™

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

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test 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 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 for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne 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 analytical methodology has identified as being present in <10% of the assayed tumor DNA.

The Report incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research.

NOTE: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

Treatment Decisions are Responsibility of Physician: Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report.

Certain sample or variant characteristics may result in reduced sensitivity. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

FoundationOne complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE