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

**PATIENT RESULTS**

- **11 genomic findings**
- **10 therapies** associated with potential clinical benefit
- **0 therapies** associated with lack of response
- **19 clinical trials**

**TUMOR TYPE: LUNG ADENOCARCINOMA**

**Genomic Alterations Identified**

- **ERBB2** amplification – equivocal
- **NF2** E427*
- **STK11** splice site 921-1G>C
- **CDKN1B** E105fs*14
- **FOXP1** E490*
- **KDM5C** W983*
- **LRP1B** loss exons 6-14
- **SPTA1** Q1346fs*3, splice site 3570-2A>T
- **TP53** I255S

**Additional Findings**

- **Tumor Mutation Burden** TMB-High; 37.53 Muts/Mb

**Additional Disease-relevant Genes with No Reportable Alterations Identified**

- **EGFR**
- **KRAS**
- **ALK**
- **BRAF**
- **MET**
- **RET**
- **ROS1**

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

* See Appendix for details

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<table>
<thead>
<tr>
<th>Genomic Findings Detected</th>
<th>FDA-Approved Therapies (in patient’s tumor type)</th>
<th>FDA-Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERBB2</strong> amplification - equivocal</td>
<td>Afatinib</td>
<td>Ado-trastuzumab emtansine Lapatinib Pertuzumab Trastuzumab</td>
<td>Yes, see clinical trials section</td>
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<tr>
<td><strong>Tumor Mutation Burden</strong> TMB-High; 37.53 Muts/ Mb</td>
<td>Nivolumab Pembrolizumab</td>
<td>Atezolizumab</td>
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<td><strong>NF2</strong> E427*</td>
<td>None</td>
<td>Everolimus Temsirolimus</td>
<td>Yes, see clinical trials section</td>
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<td><strong>STK11</strong> splice site 921-1G&gt;C</td>
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<td><strong>TP53</strong> I255S</td>
<td>None</td>
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</tbody>
</table>

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. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient’s tumor type.

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**GENOMIC ALTERATIONS**

<table>
<thead>
<tr>
<th>GENE ALTERATION</th>
<th>INTERPRETATION</th>
</tr>
</thead>
</table>
| **ERBB2** | **Gene and Alteration:** ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation.  
**Frequency and Prognosis:** In the TCGA datasets, ERBB2 amplification or mutation was observed in 6% of lung adenocarcinoma cases. HER2 overexpression has been documented in 11-32% of non-small cell lung cancers (NSCLC), and is higher in lung adenocarcinomas (38%) than in squamous cell (16%) and large cell (17.9%) tumors. A tendency toward shorter survival has been observed in patients with NSCLC harboring ERBB2 amplification and strong HER2 protein expression.  
**Potential Treatment Strategies:** Based on extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab, pertuzumab in combination with trastuzumab, emtansine (T-DM1), and ado-trastuzumab emtansine (T-DM1), as well as dual EGFR/HER2 kinase inhibitors such as lapatinib, afatinib, neratinib, and dacomitinib. In patients with breast cancer, concurrent PIK3CA or PTEN alterations that activate the PI3K pathway have been associated with resistance to therapies that target HER2, including trastuzumab and lapatinib. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alteration is associated with trastuzumab resistance, and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib. Clinical trials of agents aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90. |
| **Tumor Mutation Burden** | **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 and cigarette smoke in lung cancer, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes, and microsatellite instability (MSI). The tumor seen here harbors a high TMB. This type of mutation load has been shown to be associated with sensitivity to immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma, anti-PD-L1 therapy in urothelial carcinoma, and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer, potentially due to expression of immune-reactive neoantigens in these tumors.  
**Frequency and Prognosis:** High TMB has been reported in 8-13% of non-small cell lung cancers (NSCLCs), including 8.2-9.6% of adenocarcinomas and 8.5% of squamous cell carcinomas (SCCs) (Spigel et al., 2016; ASCO Abstract 9017, Jiang et al., 2016; ASCO Abstract e23128). High-TMB NSCLC rarely harbors known driver mutations (1% each with EGFR, ALK, ROS1, or MET), with the exception of BRAF (10.3%) or KRAS (9.4%) mutation (Spigel et al., 2016; ASCO Abstract 9017). Higher mutational load was reported to be associated with later stage NSCLC in a study of 48 African-American patients (Schwartz et al., 2016; ASCO Abstract 8533). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC (Schwartz et al., 2016; ASCO Abstract 8533), several other large studies did find a strong association with increased TMB in NSCLC and colorectal cancer. 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). |

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INTERPRETATION

**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, anti-PD-L1, and anti-PD-1 therapies. FDA-approved agents include ipilimumab, atezolizumab, 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). 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. 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 or nivolumab and 2 patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab and anti-PD-1 treatment (Johnson et al., 2016; ASCO Abstract 105). For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations (mut) per megabase (Mb)) compared to nonresponders (6.4 mut/Mb).

**Gene and Alteration:** Merlin, encoded by NF2, coordinates cell contact with growth signals; the inactivation of Merlin disrupts this mechanism and can lead to unrestrained growth despite cell contact. NF2 alterations that disrupt the FERM domain (amino acids 22-311), including in-frame deletions that disrupt the Paxillin-binding region (aa 50-70) of the FERM domain, and/or the C-terminal region (amino acids 506-547), such as observed here, are predicted to be inactivating. Heterozygous germline NF2 loss or inactivation is associated with neurofibromatosis type 2 syndrome, which results in the development of vestibular schwannomas, meningiomas, ependymomas, and ocular disturbances. Prevalence for this disorder in the general population is estimated to be 1:25,000. In the appropriate clinical context, germline testing of NF2 is recommended.

**Frequency and Prognosis:** NF2 mutation or homozygous loss is not common in lung non-small cell lung cancer (NSCLC) and has been reported in ~1% of squamous cell carcinoma and adenocarcinoma samples analyzed in the TCGA datasets. In one study, NF2 mutation has been reported in just 1/45 lung cancer cases.

**Potential Treatment Strategies:** On the basis of strong clinical evidence from multiple case reports as well as extensive preclinical evidence, NF2 inactivation may predict sensitivity to mTOR inhibitors, including approved agents everolimus and temsirolimus. Loss or inactivation of NF2 may also predict sensitivity to FAK inhibitors, based on clinical data in mesothelioma (Soria et al., 2012; ENA Abstract 610) and strong preclinical data. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib. Similarly, on the basis of limited clinical (Subbiah et al., 2011; ASCO Abstract 2100) and preclinical evidence, NF2 inactivation may predict sensitivity to MEK inhibitors, such as approved agents trametinib and cobimetinib. These and other relevant compounds are being investigated in clinical trials. A Phase 1b trial of a combination of the mTOR inhibitor everolimus and the MEK inhibitor trametinib in patients with solid tumors reported frequent adverse events and was unable to identify a recommended Phase 2 dose and schedule for the combination.

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**FOUNDATION ONE**

<table>
<thead>
<tr>
<th>GENE ALTERATION</th>
<th>INTERPRETATION</th>
</tr>
</thead>
</table>
| **STK11**       | **Gene and Alteration:** The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels\(^8\). LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis\(^85,86\). Functional disruption of the STK11 kinase domain (amino acids 49-309) or STRAD binding domain (amino acids 320-343) through mutation or loss, as observed here, is predicted to be inactivating\(^87,88,89,90,91,92,93,94,95,96,97\). Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation\(^88\). This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers\(^98,99,100\), and individuals with this syndrome have a 30-50% risk of developing breast cancer\(^98,100\). Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.  
**Frequency and Prognosis:** Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)\(^51,68,101,102,103,104,105\). STK11 mutations in NSCLC often co-occur with activating KRAS mutations\(^104,105\). In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas\(^102\). Decreased expression of LKB1 correlates with poor prognosis and/or higher histological grade in patients with some cancer types, although prognosis in patients with NSCLC is not known\(^106,107\).  
**Potential Treatment Strategies:** Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations\(^84,102,108,109,110\). The mTOR inhibitors everolimus and temsirolimus are FDA approved for the treatment of other tumor types, and are being investigated in clinical trials for several indications\(^111,112,113,114\). A PJS patient with pancreatic cancer and an STK11 mutation experienced a partial response to the mTOR inhibitor everolimus\(^115\). Loss of STK11 also leads to activation of the downstream kinase SRC, suggesting that inhibitors such as dasatinib or bosutinib may be relevant for the treatment of LKB1-deficient tumors\(^85\). |

| **CDKN1B** | **Gene and Alteration:** CDKN1B encodes the cyclin-dependent kinase inhibitor p27, which controls cell cycle progression through G1 phase by binding to prevent action of cyclin E/CDK2 and cyclin D/CDK4 protein complexes. Removal of this inhibition is required for cellular transition from quiescence to a proliferative state. There is some evidence that germline variants in CDKN1B are associated with increased risk for several tumor types, including prostate\(^116\), endometrial\(^117\), and colorectal cancers\(^118\).  
**Frequency and Prognosis:** Somatic inactivating mutations in CDKN1B have been documented in fewer than 1% of tumors (COSMIC, 2016). A survey of 350 breast cancers found somatic mutations in CDKN1B in approximately 1% of cases\(^119\). Mutations in p27 have been associated with multiple endocrine neoplasia syndrome, and truncating alterations have been shown to disrupt normal subcellular localization of p27 due to the loss of a nuclear localization motif\(^120,121\). Loss of p27 expression has been described in some studies as a negative indicator of prognosis in patients with B-cell lymphomas, but the relationship between p27 levels and cell proliferation is somewhat controversial\(^122\). Changes in the levels of p27 have been observed in the context of multiple myeloma, and decreased levels of p27 are associated with reduced overall survival and more aggressive cancers\(^123,124,125\). A preclinical study showed that p27 is essential for cell cycle arrest of T-cell acute lymphoblastic leukemia (T-ALL) cells by glucocorticoid treatment\(^126\). |

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## INTERPRETATION

### Potential Treatment Strategies:

There are no targeted therapies available to address genomic alterations in CDKN1B.

### FOXP1

**Gene and Alteration:** FOXP1 encodes the protein 'forkhead box protein P1', a transcription factor previously reported as a tumor suppressor, but one which can also function as an oncogene when shorter isoforms are expressed\(^{127,128}\).  

**Frequency and Prognosis:** Loss of FOXP1 expression has been reported to be a frequent event in endometrial cancer\(^{129}\). FOXP1 translocations have been described in acute lymphoblastic leukemia\(^{130,131}\), and deletions of the chromosomal region where FOXP1 is located have been reported in acute myeloid leukemia and myeloproliferative neoplasms\(^{132,133}\). Genomic rearrangements that disrupt the 5' regulatory region of FOXP1 have been detected and characterized in several lymphomas\(^{134,135,136}\). Such alterations have been demonstrated to result in expression of N-terminally truncated variants of FOXP1, or aberrant expression of full length FOXP1 driven by strong regulatory elements, such as IGH, as observed in the t(3;14)(p13;q32) translocation\(^{107}\). In a genome-wide association study, polymorphisms at the FOXP1 locus were found to be significantly associated with Barrett esophagus and esophageal adenocarcinoma\(^{138}\). Conflicting data have been presented on the prognostic impact of FOXP1 expression, as high expression of FOXP1 is associated with poor prognosis in patients with cutaneous large B-cell lymphomas or mucosal tissue-associated lymphoid tissue (MALT) lymphomas, but improved prognosis in patients with breast or lung cancer\(^{134,135,139,140,141}\).  

**Potential Treatment Strategies:** There are no approved therapies available to address alterations in FOXP1.

### KDM5C

**Gene and Alteration:** KDM5C encodes a histone lysine demethylase that acts, along with related histone-modifying enzymes, to control gene expression in response to developmental and environmental cues\(^{142}\). In addition to its role as a histone-modifying demethylase, KDM5C has been suggested to play a role in regulation of the SMAD3 signal transduction response to TGF-beta, a role that would be consistent with function as a tumor suppressor\(^{143}\). Germline inactivating mutations in KDM5C cause an X-linked intellectual disability syndrome also characterized by short stature and hyperreflexia\(^{144}\).  

**Frequency and Prognosis:** Somatic mutations of KDM5C have been observed in a number of solid tumors and the role of KDM5C inactivation has been well characterized in clear cell renal cell carcinoma (ccRCC)\(^{145,146,147,148}\). However, KDM5C amplification and overexpression has been implicated in prostate cancer where KDM5C has been associated with poor prognosis\(^{149}\).  

**Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in KDM5C.
**Gene and Alteration**: LRPIB encodes the low-density lipoprotein receptor-related protein 1B, also called LRPDIT. LRPIB is subject to frequent mutation, deletion, and/or silencing in cancers, leading to the hypothesis that it behaves as a tumor suppressor. However, the mechanism of tumor suppression is unclear. The LRPIB protein consists of three regions: an extracellular LDL-receptor (amino acids 25-4444), a transmembrane region (4445-4467), and a smaller cytoplasmic portion (4468-4599). Somatic mutations that lead to C-terminal truncation of LRPIB are common, and in vitro studies suggest that an intracellular domain fragment released by a gamma-secretase-like activity translocates to the nucleus where it suppresses anchorage-independent cell growth. In addition, heterozygous mice that express a C-terminally truncated LRPIB missing codons 3457-4599, which includes the transmembrane and cytoplasmic domain were reported to be viable, with no phenotype; however, mice homozygous for the mutation or the null mutation were inviable. Therefore, it is possible that truncated proteins are still functional.

**Frequency and Prognosis**: LRPIB mutations have been frequently reported in many types of cancer, including 12-16% of multiple myeloma, 6% of diffuse large B-cell lymphoma, 3% of chronic lymphocytic leukemia/small cell lymphoma, 1% of acute myeloid leukemia, and 7% (2/29) of chronic myeloid leukemia cases (COSMIC, 2016). In addition, LRPIB mutations have been frequently reported in many solid tumors: 32% of melanoma, 30-39% of squamous cell lung cancer, 28-32% of lung adenocarcinoma, 26% of stomach cancer, and 6-20% of head and neck squamous cell carcinoma, bladder cancer, and colorectal cancer cases (cBioPortal, 2016). LRPIB is commonly inactivated in non-small cell lung cancer cell lines, and low expression of LRPIB mRNA was associated with poor patient outcome.

**Potential Treatment Strategies**: There are no therapies or clinical trials that address the loss or mutation of LRPIB in cancer. In some tumor types, such as high-grade serous cancer (HGSC), LRPIB deletion has been reported to be associated with resistance to liposomal doxorubicin.

**Gene and Alteration**: SPTA1 encodes the protein spectrin alpha chain 1, a component of the cytoskeleton of erythrocytes. Germline mutations in SPTA1 have been associated with disorders featuring abnormally shaped erythrocytes, such as elliptocytosis and spherocytosis.

**Frequency and Prognosis**: SPTA1 mutations have been found in 9% of glioblastoma samples analyzed in one study, and mutations have been reported with high prevalence in melanoma, lung tumors, and esophageal tumors (COSMIC, cBioPortal, 2016).

**Potential Treatment Strategies**: There are no therapies available to directly address genomic alterations in SPTA1 in cancer.

**Gene and Alteration**: Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. Mutations affecting the DNA binding domain (aa 100-292), the tetramerization domain (aa 325-356), or the C-terminal regulatory domain (aa 356-393), such as observed here, are thought to disrupt the transactivation of p53-dependent genes and are predicted to promote tumorigenesis. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000 to 1:20,000, and in the appropriate clinical context, germline testing of TP53 is recommended.
**Gene Alteration**

**Interpretation**

**Frequency and Prognosis:** TP53 is one of the most commonly mutated genes in lung cancer, and mutations in this gene have been reported in 43-80% of non-small cell lung cancers (NSCLCs) and specifically in 45% of lung adenocarcinoma samples. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma.

**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, therapies that reactivate mutant p53 such as APR-246, or p53 gene therapy and immunotherapeutics such as SGT-53 and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). 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 1 clinical trial, 8 of 11 evaluable patients receiving SGT-53 as a single agent exhibited stable disease. Clinical trials of SGT-53 in combination with chemotherapy are underway. 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 xenograft mouse model. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are underway for some tumor types for patients with a TP53 mutation.
<table>
<thead>
<tr>
<th>THERAPY</th>
<th>SUMMARY OF DATA IN PATIENT TUMOR TYPE</th>
</tr>
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</table>
| Afatinib | **Approved Indications**: Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients with EGFR exon 19 deletions or exon 21 (L858R) missense mutations.  
**Gene Association**: ERBB2 amplification or activating mutations may indicate sensitivity to afatinib on the basis of clinical evidence in various solid tumors\(^{11,19,193}\).  
**Supporting Data**: Phase 3 clinical trials have demonstrated that treatment with afatinib, compared to chemotherapy, leads to significantly increased progression-free survival for patients with EGFR-mutant NSCLC\(^{194,195}\), and increased overall survival (OS) for patients with EGFR exon 19 alterations specifically\(^{196}\). A Phase 3 trial comparing afatinib with erlotinib as second-line therapies for advanced lung squamous cell carcinoma reported significantly higher OS (7.9 months vs. 6.8 months) and disease control rate (DCR) (51% vs. 40%) for patients treated with afatinib\(^{197}\). Phase 2/3 studies of afatinib treatment for patients with erlotinib- or gefitinib-resistant NSCLC have generally reported partial responses (PRs) of only 7-9%\(^{22,198,199,200,201,202}\) and DCRs of more than 50%\(^{22}\); in particular, disease control was achieved for 2/2 patients with EGFR-amplified NSCLC\(^22\) and 9/14 patients with T790M-positive NSCLC\(^{202}\). The T790M mutation has been implicated in reduced response to afatinib\(^{201,203,204}\), with a secondary T790M mutation reported in 48% (20/42) of patients with afatinib-resistant lung adenocarcinoma\(^{203}\). The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease\(^{205}\), including T790M-positive cases\(^{205,206}\), although adverse reactions may be a concern with this combination\(^207\). Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel\(^{208}\). |
| 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 FDA 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 non-small cell lung cancer (NSCLC) following disease progression on prior treatments, advanced renal cell carcinoma following antiangiogenic therapy, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.  
**Gene Association**: On the basis of emerging clinical data in patients with non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017\(^{38}\), colorectal cancer\(^{46}\), or melanoma (Johnson et al., 2016; ASCO Abstract 105) and case reports in endometrial cancer\(^{53,54}\) and glioblastoma\(^{55}\), high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as nivolumab.  

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Supporting Data: Studies investigating the use of nivolumab as first-line treatment for patients with non-small cell lung carcinoma (NSCLC) reported an objective response rate (ORR) of 23% (12/53), median overall survival (OS) of 19.4 months, and 1-year OS rate of 73% with monotherapy209. Combinations with platinum-based doublet chemotherapy (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%210. In patients with platinum-refractory non-squamous NSCLC, nivolumab improved median OS (12.2 vs. 9.4 months) and the ORR (19% vs. 12%) compared with docetaxel; PD-L1 expression was associated with benefit from nivolumab in this study (OS hazard ratios of 0.40-0.59)211. In patients with previously treated squamous NSCLC, nivolumab resulted in longer median OS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel, and PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy211,213. Real-world studies of nivolumab for the treatment of NSCLC reported clinical benefit for 35-36% of patients (Crino et al., 2016; ASCO Abstract 3067, Corny et al., 2016; ASCO Abstract e20633). A Phase 1 study of nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg, every 6 or 12 weeks) as first-line treatment for advanced NSCLC resulted in ORRs of 31-39% and median PFS of 8.0-8.3 months (Hellmann et al., 2016; ASCO Abstract 3001). Nivolumab in combination with erlotinib for the treatment of chemotherapy-naive EGFR-mutant NSCLC achieved an ORR of 19%; additionally, 15% (3/20) partial responses (PR) 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)214. A small 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 FDA approved to treat unresectable or metastatic melanoma and PD-L1-positive metastatic non-small cell lung cancer (NSCLC) refractory to prior therapy.

Gene Association: On the basis of emerging clinical data in patients with non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017)218, colorectal cancer46, or melanoma (Johnson et al., 2016; ASCO Abstract 105) and case reports in endometrial cancer53,54 and glioblastoma55, high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

Supporting Data: In a Phase 2/3 study for previously treated NSCLC with PD-L1 expression (on at least 1% of tumor cells), pembrolizumab extended median overall survival (OS) (10.4-12.7 vs 8.2 months) when compared with docetaxel215. A Phase 1 study of pembrolizumab in NSCLC reported an overall response rate (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, Garon et al., 2016; ASCO Abstract 9024)216. In both studies, pembrolizumab demonstrated greater efficacy in patients with PD-L1 expression on at least 50% of tumor cells, with ORRs (29-45%)215,216, median OS (14.9-17.3 months)215, and progression-free survival (PFS; 5.0-6.3 months)215,216 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) of patients experienced brain metastases responses217. As first-line therapy for patients with EGFR/ALK wild-type advanced NSCLC, pembrolizumab plus platinum doublet chemotherapy (carboplatin/paclitaxel, carboplatin/paclitaxel/bevacizumab, or carboplatin/pemetrexed) achieved ORRs of 52% (13/25) and 59% (29/49) for patients with any histology or with nonsquamous NSCLC, respectively (Gadgeel et al., 2016; ASCO Abstract 9016). Pembrolizumab combined with the anti-CTLA4 antibody ipilimumab for patients with recurrent advanced NSCLC and at least one previous treatment reported an ORR of 24%, stable disease rate of 40% (18/45), and median OS of 17 months (Gubens et al., 2016; ASCO Abstract 9027). A Phase 1 study of pembrolizumab in combination with the anti-4-1BB antibody utomilumab reported a partial response for 1 out of 6 cases with NSCLC (Tolcher et al., 2016; ASCO Abstract 3002).

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Electronically Signed by Jeffrey S. Ross, M.D. | Jeffrey S. Ross, M.D., Medical Director | CLIA Number: 22D027531 | 10 August 2016
Foundation Medicine, Inc., 150 2nd Street, 1st Floor, Cambridge, MA 02141 | 1-888-988-3639 page 10 of 38
## ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>SUMMARY OF DATA IN OTHER TUMOR TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-trastuzumab</td>
<td><strong>Approved Indications:</strong> Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling(^{218,219}); it also releases the cytotoxic therapy DM1 into cells, leading to cell death(^{219,220}). T-DM1 is FDA approved for the treatment of HER2-positive (HER2+) metastatic breast cancer.</td>
</tr>
<tr>
<td></td>
<td><strong>Gene Association:</strong> ERBB2 activating mutations or amplification may predict sensitivity to T-DM1.</td>
</tr>
<tr>
<td>Lapatinib</td>
<td><strong>Approved Indications:</strong> Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capcitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.</td>
</tr>
<tr>
<td></td>
<td><strong>Gene Association:</strong> Activation or amplification of ERBB2 may predict sensitivity to lapatinib. In one study, a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations, but without ERBB2 amplification or protein overexpression, experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab(^{14}).</td>
</tr>
<tr>
<td></td>
<td><strong>Supporting Data:</strong> Investigations into the efficacy of lapatinib have primarily been in the context of preclinical assays, lapatinib reduced cell proliferation in vitro and reduced the number and size of tumors in mouse xenograft models of EGFR- and ERBB2-amplified non-small cell lung cancer (NSCLC) cells(^{227}). A Phase 1 study of single-agent lapatinib included 9 unselected patients with lung cancer and reported 1 case of prolonged stable disease(^{228}). In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted(^{229}).</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td><strong>Approved Indications:</strong> Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat a subset of patients with HER2-positive (HER2+) breast cancer(^{12}).</td>
</tr>
<tr>
<td></td>
<td><strong>Gene Association:</strong> ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab.</td>
</tr>
</tbody>
</table>
Supporting Data: In a Phase 1 study of pertuzumab in advanced cancer, 2/19 patients reported partial responses and 6/19 patients reported stable disease after two cycles, including one patient with lung cancer. In another Phase 1 study in Japanese patients with solid tumors, no responses were observed and stable disease was reported in 1 of 7 patients with NSCLC. In a Phase 2 study of pertuzumab in NSCLC, no responses were observed and the progression-free survival was 6.1 weeks. Phase 1 and 2 trials of pertuzumab in combination with erlotinib in NSCLC have reported a response rate of 20% (3/15, 2 of the responders had mutant EGFR); a reduction in circulating tumor cells was noted and correlated with reduction in tumor size. In a Phase 2 study of pertuzumab plus erlotinib in relapsed patients with NSCLC, PET-CT imaging showed that the primary endpoint of response rate (RR) was met in 19.5% of all patients (n = 41) and in 8.7% of patients with wild-type EGFR NSCLC (n = 23); however, 68.3% (28/41) of patients showed treatment-related grade 3 (or higher) adverse events.

Trastuzumab

Approved Indications: Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved for the treatment of breast cancers or metastatic gastric or gastroesophageal adenocarcinomas that overexpress HER2.

Gene Association: ERBB2 amplification or activating mutations may confer sensitivity to trastuzumab. Trastuzumab-involving regimens elicited significant responses in patients with NSCLC and ERBB2 exon 20 insertions (8 partial responses (PRs) and 4 stable disease vs. 1 progressive disease) and in a patient with breast cancer harboring ERBB2 V777L and S310F activating mutations. A patient with HER2-positive parotid salivary duct carcinoma also reported a PR following treatment with trastuzumab in combination with carboplatin and docetaxel.

Supporting Data: A Phase 2 clinical trial of docetaxel with trastuzumab in non-small cell lung cancer (NSCLC) reported partial responses in 8% of patients; response did not correlate with HER2 status as assessed by immunohistochemistry. Another Phase 2 study of 169 patients with NSCLC reported an objective response rate of 23% (7/30 patients) in the patients treated with a combination therapy of docetaxel and trastuzumab, and 32% (11/34) in patients treated with paclitaxel and trastuzumab. HER2 expression did not impact the results of this study. A patient with lung adenocarcinoma that was HER2-positive by FISH and harbored an ERBB2 G776L mutation experienced a partial response on trastuzumab and paclitaxel. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy.

Atezolizumab

Approved Indications: Atezolizumab 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 with advanced urothelial carcinoma who progress during or following platinum-based chemotherapy.

Gene Association: On the basis of emerging clinical data in patients with urothelial carcinoma, non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017), or melanoma (Johnson et al., 2016; ASCO Abstract 105), high tumor mutation burden (TMB) may predict sensitivity to anti-PD-L1 therapies such as atezolizumab.
Supporting Data: A Phase 2 study of atezolizumab for the treatment of non-small cell lung carcinoma (NSCLC) reported significantly improved median overall survival (OS; 12.6 vs. 9.7 months) and objective response duration (18.6 vs. 7.2 months) when compared with docetaxel; PD-L1 expression correlated with improved response to atezolizumab (median OS 15.1 vs. 9.7 months) (Smith et al., 2016; ASCO Abstract 9028). 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. Atezolizumab achieved similar ORRs for patients with NSCLC who received no prior chemotherapy (19-29%), progressed on previous platinum therapy (17-27%), or had brain metastases or treated asymptomatic brain metastases (17%) (Besse et al., 2015; ECC Abstract 16LBA, Spigel et al., 2015; ASCO Abstract 8028).

Everolimus

Approved Indications: Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomylipoma and subependymal giant cell astrocytoma. Everolimus is also approved to treat hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane following prior therapy with letrozole or anastrozole, as well as in combination with the multikinase inhibitor lenvatinib to treat advanced RCC following prior antiangiogenic therapy.

Gene Association: Preclinical data suggests that loss or inactivation of NF2 may be associated with sensitivity to rapamycin, which is similar in mechanism of action to everolimus. Several case reports describe durable complete or partial responses of patients with NF2-mutant solid tumors to therapy regimens including everolimus or temsirolimus. Increased mTOR signaling is present in LKB1-deficient tumors; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations. Clinical responses to everolimus have been reported in patients with pancreatic cancer and STK11 alterations, with two patients exhibiting a partial response for more than 6 months (Moreira et al., 2015; ASCO Abstract 315).

Supporting Data: A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity, but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population (Khuri et al., 2011; ASCO Abstract e13601). A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel as bevacizumab in advanced NSCLC and found the combinations produced 1 complete response and 10 partial responses (n=52), although treatments were not well tolerated. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing stable disease (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses. A trial of combination treatment with sorafenib and everolimus that included 2 patients with lung adenocarcinoma reported a partial response in one patient and stable disease in the other, with both patients experiencing progression-free survival of more than 4 months. A Phase 1b trial of a combination of everolimus and the MEK inhibitor trametinib in patients with solid tumors reported frequent adverse events and the study was unable to identify a recommended Phase 2 dose and schedule for the combination.

Temsirolimus

Approved Indications: Temsirolimus is an intravenous mTOR inhibitor that is FDA approved to treat advanced renal cell carcinoma.

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**Gene Association:** Preclinical data suggests that loss or inactivation of NF2 may be associated with sensitivity to rapamycin, which has a similar mechanism of action to temsirolimus\(^{24,75}\). Several case reports describe durable complete or partial responses of patients with NF2-mutant solid tumors to therapy regimens including everolimus or temsirolimus\(^{70,71,72,73}\). Increased mTOR signaling is present in LKB1-deficient tumors\(^{84,102,108,110,241}\); therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations\(^{84}\).

**Supporting Data:** In a Phase 2 clinical trial in NSCLC, front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point\(^{247}\). In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited a partial response, and 2 exhibited stable disease\(^{248}\).

Genomic alterations detected may be associated with activity of certain approved drugs; however, the agents listed in this report may have little or no evidence in the patient’s tumor type.
**CLINICAL TRIALS TO CONSIDER**

**GENE**

**RATIONALE FOR POTENTIAL CLINICAL TRIALS**

ERBB2 amplification or activating mutations may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of chemotherapy or other targeted therapies, such as HSP90 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](http://clinicaltrials.gov) using keyword terms such as "ERBB2", "HER2", "trastuzumab", "lapatinib", "pertuzumab", "ado-trastuzumab emtansine", "afatinib", "HSP90", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

<table>
<thead>
<tr>
<th>TITLE</th>
<th>PHASE</th>
<th>TARGETS</th>
<th>LOCATIONS</th>
<th>NCT ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I Active Immunotherapy Trial With a Combination of Two Chimeric (Trastuzumab-like and Pertuzumab-like) Human Epidermal Growth Factor Receptor 2 (HER-2) B Cell Peptide Vaccine Emulsified in ISA 720 and Normal Adjuvant in Patients With Advanced Solid Tumors</td>
<td>Phase 1</td>
<td>ERBB2</td>
<td>Ohio</td>
<td>NCT01376505</td>
</tr>
<tr>
<td>An Open-label, Multicenter, Multinational, Phase 2 Study Exploring the Efficacy and Safety of Neratinib Therapy in Patients With Solid Tumors With Activating HER2, HER3 or EGFR Mutations or With EGFR Gene Amplification.</td>
<td>Phase 2</td>
<td>EGFR, ERBB2, ERBB4</td>
<td>California, Florida, Massachusetts, Missouri, New Jersey, New York, Tennessee, Texas, Barcelona (Spain), Cremona (Italy), Helsinki (Finland), London (United Kingdom), Madrid (Spain), Petch Tiqwa (Israel), Rehovot (Israel), Seoul (Korea, Republic of), Torino (Italy), Valencia (Spain), Victoria (Australia)</td>
<td>NCT01953926</td>
</tr>
<tr>
<td>Targeted Agent and Profiling Utilization Registry (TAPUR) Study</td>
<td>Phase 2</td>
<td>ALK, Others</td>
<td>Michigan, North Carolina</td>
<td>NCT02693535</td>
</tr>
<tr>
<td>My Pathway: An Open Label Phase Ia Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents</td>
<td>Phase 2</td>
<td>EGFR, ERBB2, BRAF, SMO</td>
<td>Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington</td>
<td>NCT02091141</td>
</tr>
<tr>
<td>Phase I Trial Evaluating Safety and Tolerability of the Irreversible Epidermal Growth Factor Receptor Inhibitor Afatinib (BIBW 2992) in</td>
<td>Phase 1</td>
<td>EGFR, ERBB2, KIT, PDGFRs, SRC, ABL</td>
<td>Florida</td>
<td>NCT01999985</td>
</tr>
</tbody>
</table>

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| Combination With the SRC Kinase Inhibitor Dasatinib for Patients With Non-small Cell Lung Cancer (NSCLC) |
|---|---|---|

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**GENE**

**Tumor Mutation Burden**
TMB-High; 37.53 Muts/Mb

**RATIONALE FOR POTENTIAL CLINICAL TRIALS**
High 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", "CT-011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

<table>
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<th>PHASE</th>
<th>TARGETS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A Phase II Trial of Concurrent Chemoradiation With Consolidation Pembrolizumab (MK-3475) for the Treatment of Inoperable or Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC): HCRN LUN14-179</td>
<td>Phase 2</td>
<td>PD-1</td>
<td>California, Indiana, Nebraska, New Jersey</td>
<td>NCT02343952</td>
</tr>
<tr>
<td>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</td>
<td>Phase 3</td>
<td>PD-L1</td>
<td>California, Connecticut, Florida, Georgia, Illinois, Indiana, Kentucky, Michigan, Nebraska, Oregon, Pennsylvania, Texas, Virginia, Washington, Wisconsin, Aichi (Japan), Alicante (Spain), Barcelona (Spain), Bunkyo-ku (Japan), Burgos (Spain), Creteil (France), Guipuzcoa (Spain), Hiroshima (Japan), Hokkaido (Japan), Hyogo (Japan), Ishikawa (Japan), Kagoshima (Japan), Kanagawa (Japan), La Coruña (Spain), Limoges (France), Malaga (Spain), Michalovce (Slovakia), Navarra (Spain), Niigata (Japan), Osaka (Japan), Piemonte (Italy), Saga (Japan), Tokyo (Japan), Yamaguchi (Japan)</td>
<td>NCT02657434</td>
</tr>
<tr>
<td>A Randomized, Double-Blind, Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)</td>
<td>Phase 3</td>
<td>PD-1</td>
<td>California, Illinois, Maryland, Massachusetts, New York, North Carolina, South Carolina, Moscow (Russian Federation), North Ryde (Australia)</td>
<td>NCT02775435</td>
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</table>

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<table>
<thead>
<tr>
<th>Study Description</th>
<th>Phase</th>
<th>Tumor Type</th>
<th>NCT Number</th>
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<tbody>
<tr>
<td>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)</td>
<td>Phase 3</td>
<td>Lung adenocarcinoma</td>
<td>NCT02477826</td>
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<tr>
<td>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 4 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks</td>
<td>Phase 3</td>
<td>PD-1</td>
<td>Arizona, California, Colorado, Florida, Illinois, Maryland, Nebraska, New York, Ohio, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, multiple ex-US locations</td>
</tr>
<tr>
<td>A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Docetaxel in Patients With Non-Small Cell Lung Cancer After Failure With Platinum-Containing Chemotherapy [IMpower210]</td>
<td>Phase 3</td>
<td>PD-L1</td>
<td>Changchun (China), Daegu (Korea, Republic of), Daejeon (Korea, Republic of), Guangzhou (China), Hangzhou (China), Jeollanam-do (Korea, Republic of), Seoul (Korea, Republic of), Shanghai (China), Tianjin (天津) (China)</td>
</tr>
</tbody>
</table>

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**NF2 E427**

Inactivation or loss of NF2 results in the dysregulation of mTOR and FAK pathway signaling. Therefore, mTOR and/or FAK inhibitors may be relevant for patients with NF2 inactivating mutations.

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 "NF2", "mTOR", "FAK", "everolimus", "temsirolimus", "GSK2256098", "VS-4718", "defactinib", "NSCLC", "lung", "solid tumor" and/or "advanced cancer".

<table>
<thead>
<tr>
<th>TITLE</th>
<th>PHASE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A Phase I Study of BKM120 and Everolimus in Advanced Solid Malignancies</td>
<td>Phase 1</td>
<td>PI3K, mTOR</td>
<td>Georgia</td>
<td>NCT01470209</td>
</tr>
<tr>
<td>A Phase I Study of VS-4718, a Focal Adhesion Kinase Inhibitor, in Subjects With Metastatic Non-Hematologic Malignancies</td>
<td>Phase 1</td>
<td>FAK</td>
<td>Arizona, California, Florida, Tennessee</td>
<td>NCT01849744</td>
</tr>
<tr>
<td>A Phase Ib/Ila Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers</td>
<td>Phase 1/Phase 2</td>
<td>mTORC1, mTORC2, MEK</td>
<td>London (United Kingdom)</td>
<td>NCT02583542</td>
</tr>
<tr>
<td>Phase II Study of Everolimus in Patients With Advanced Solid Malignancies With TSC1 and TSC2 Mutations</td>
<td>Phase 2</td>
<td>mTOR</td>
<td>Missouri</td>
<td>NCT02352844</td>
</tr>
<tr>
<td>A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies</td>
<td>Phase 1</td>
<td>PI3K-alpha, mTORC1, mTORC2</td>
<td>Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)</td>
<td>NCT01899053</td>
</tr>
</tbody>
</table>
STK11 splice site 921-1G>C

STK11 loss or inactivating mutations may predict sensitivity to mTOR inhibitors or SRC 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 "mTOR", "SRC", "everolimus", "temsirolimus", "dasatinib", "bosutinib", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

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<td>A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies</td>
<td>Phase 1</td>
<td>PI3K-alpha, mTORC1, mTORC2</td>
<td>Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)</td>
<td>NCT01899053</td>
</tr>
<tr>
<td>Phase I Trial Evaluating Safety and Tolerability of the Irreversible Epidermal Growth Factor Receptor Inhibitor Afatinib (BIBW 2992) in Combination With the SRC Kinase Inhibitor Dasatinib for Patients With Non-small Cell Lung Cancer (NSCLC)</td>
<td>Phase 1</td>
<td>EGFR, ERBB2, KIT, PDGFRs, SRC, ABL</td>
<td>Florida</td>
<td>NCT01999985</td>
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<tr>
<td>Phase I Study of MLN0128 (NSC# 768435) in Combination With Ziv-Aflibercept (NSC# 724770) in Patients With Advanced Cancers</td>
<td>Phase 1</td>
<td>mTORC1, mTORC2</td>
<td>Texas</td>
<td>NCT02159989</td>
</tr>
<tr>
<td>A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies</td>
<td>Phase 1</td>
<td>mTORC1, mTORC2</td>
<td>Florida, Oklahoma, Tennessee</td>
<td>NCT02412722</td>
</tr>
</tbody>
</table>
APPENDIX

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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
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<tbody>
<tr>
<td>AKT3</td>
<td>E115K</td>
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<tr>
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<td>L471M</td>
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<tr>
<td>GPR124</td>
<td>Q227K,V688L</td>
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<tr>
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<td>MS-Stable</td>
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<tr>
<td>PRDM1</td>
<td>amplification</td>
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<tr>
<td>WISP3</td>
<td>amplification</td>
</tr>
<tr>
<td>ARAF</td>
<td>G446D</td>
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<tr>
<td>EPFA5</td>
<td>N120K</td>
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<tr>
<td>HSD3B1</td>
<td>V224_V226&gt;G*CV, Y225C</td>
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<tr>
<td>MLL2</td>
<td>Q3738H</td>
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HENES 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

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DNA Gene List: For the Detection of Select Rearrangements

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Additional Assays: For the Detection of Select Cancer Biomarkers

Microsatellite status
Tumor Mutation Burden

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**Sensitivity:**

- **Base Substitutions:** At Mutant Allele Frequency ≥10% >99.9% (CI* 99.6%-100%)
- **Insertions/Deletions (1-40 bp):** At Mutant Allele Frequency 5-10% 99.3% (CI* 98.3%-99.8%)
- **Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥28):** At ≥30% tumor nuclei >99.0% (CI* 93.6%-100%)
- **Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions):** At ≥30% tumor nuclei 97.2% (CI* 85.5%-99.9%)
- **Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei):**
  - At ≥20% tumor nuclei >90.0%
  - ≥99.0% for ALK fusion2
  - (CI* 89.1%-100%)

**Specificity:**

- **all variant types:** Positive Predictive Value (PPV) >99.0%
- **Microsatellite status:** Positive Predictive Value (PPV) >95.0%
- **Tumor Mutation 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 mutation burden precision

*95% Confidence Interval

** 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.


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 (a measure of microsatellite instability, or “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 assessed for all FoundationOne samples. MSI-High results are reported in all tumor types. In select tumor types, other Microsatellite status results may be reported (MS-Stable, MSI-Ambiguous, MSI-Unknown) when relevant. Microsatellite status result may be reported as “Unknown” if the sample is not of sufficient quality to confidently determine Microsatellite status.

Tumor Mutation 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. TMB-High results are reported in all tumor types. In select tumor types, other TMB results may be reported (TMB-Intermediate, TMB-Low, TMB-Unknown) when relevant. TMB results 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 less than or equal to 5 Muts/Mb. Tumor Mutation Burden may be reported as “Unknown” if the sample is not of sufficient quality to confidently determine Tumor Mutation 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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75 James MF, Han S, Polizzano C, et al. (2009) NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with menigioma and schwannoma growth. Mol Cell Biol 29(15):4250-61.


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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.

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