



Date of Birth

Sex

Male

Medical Facility

Ordering Physician

FMI Case #

Additional Recipient

Medical Record #

Medical Facility ID #

Specimen ID

Pathologist

Specimen Received

Specimen Site

Lymph Node

Date of Collection

Specimen Type

ABOUT THE TEST:

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

THERAPEUTIC IMPLICATIONS

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Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
ERBB2 amplification - equivocal	Afatinib	Ado-trastuzumab emtansine Lapatinib Pertuzumab Trastuzumab	Yes, see clinical trials section
Tumor Mutation Burden TMB-High; 37.53 Muts/Mb	Nivolumab Pembrolizumab	Atezolizumab	Yes, see clinical trials section
NF2 E427*	None	Everolimus Temozolomide	Yes, see clinical trials section
STK11 splice site 921-1G>C	None	Everolimus Temozolomide	Yes, see clinical trials section
CDKN1B E105fs*14	None	None	None
FOXP1 E490*	None	None	None
KDM5C W983*	None	None	None
LRP1B loss exons 6-14	None	None	None
SPTA1 Q1346fs*3, splice site 3570-2A>T	None	None	None
TP53 I255S	None	None	None

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

GENE ALTERATION	INTERPRETATION
<p>● ERBB2</p> <p>amplification - equivocal</p>	<p>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 formation¹.</p> <p>Frequency and Prognosis: In the TCGA datasets, ERBB2 amplification or mutation was observed in 6% of lung adenocarcinoma cases². 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^{3,4}. A tendency toward shorter survival has been observed in patients with NSCLC harboring ERBB2 amplification and strong HER2 protein expression⁵.</p> <p>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^{6,7,8,9,10,11}, pertuzumab in combination with trastuzumab^{8,12,13}, and ado-trastuzumab emtansine (T-DM1)¹⁴, as well as dual EGFR/HER2 kinase inhibitors such as lapatinib^{15,16,17,18}, afatinib^{11,19,20,21,22}, neratinib^{23,24}, and dacomitinib²⁵. 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^{26,27,28,29,30}. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alteration is associated with trastuzumab resistance³¹, and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib³². Clinical trials of agents aimed at preventing or overcoming resistance to anti-HER2 therapies are under way, including agents targeting the PI3K-AKT pathway or HSP90^{33,34}.</p>
<p>● Tumor Mutation Burden</p> <p>TMB-High; 37.53 Muts/Mb</p>	<p>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^{35,36} and cigarette smoke in lung cancer^{37,38}, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes^{39,40,41,42,43}, and microsatellite instability (MSI)^{39,42,43}. 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 melanoma⁴⁴, anti-PD-L1 therapy in urothelial carcinoma⁴⁵, and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer^{38,46}, potentially due to expression of immune-reactive neoantigens in these tumors³⁸.</p> <p>Frequency and Prognosis: High TMB has been reported in 8-13% of non-small cell lung carcinomas (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)^{47,48}, several other large studies did find a strong association with increased TMB^{49,50,51,52}. 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)⁴⁷.</p>

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GENE
ALTERATION

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-4⁴⁴, anti-PD-L1⁴⁵, and anti-PD-1 therapies^{38,46}; 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)³⁸. 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^{38,46}. 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 pembrolizumab⁵³ or nivolumab⁵⁴ and two patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab⁵⁵. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab^{44,56} 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)⁴⁵.

● **NF2**
E427*

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 contact⁵⁷. 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 domain⁵⁸, and/or the C-terminal region (amino acids 506-547), such as observed here, are predicted to be inactivating^{58,59,60,61,62,63,64}. 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^{65,66,67}. Prevalence for this disorder in the general population is estimated to be 1:25,000⁶⁷. 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^{2,68}. In one study, NF2 mutation has been reported in just 1/45 lung cancer cases⁶⁹.

Potential Treatment Strategies: On the basis of strong clinical evidence from multiple case reports^{70,71,72,73} as well as extensive preclinical evidence^{74,75}, 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^{76,77}. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib^{78,79}. Similarly, on the basis of limited clinical (Subbiah et al., 2011; ASCO Abstract 2100) and preclinical^{80,81,82} 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 combination⁸³.

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GENE
ALTERATION

INTERPRETATION

● **STK11**

splice site 921-1G>C

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 levels⁸⁴. 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 formation⁹⁸. 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 carcinomas¹⁰². 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 everolimus¹¹⁵. 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 tumors⁸⁵.

● **CDKN1B**

E105fs*14

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 prostate¹¹⁶, endometrial¹¹⁷, and colorectal cancers¹¹⁸.

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 cases¹¹⁹. 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 controversial¹²². 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 treatment¹²⁶.

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GENE ALTERATION	INTERPRETATION
	<p>Potential Treatment Strategies: There are no targeted therapies available to address genomic alterations in CDKN1B.</p>
<p>● FOXP1 E490*</p>	<p>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}.</p> <p>Frequency and Prognosis: Loss of FOXP1 expression has been reported to be a frequent event in endometrial cancer¹²⁹. 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) translocation¹³⁷. In a genome-wide association study, polymorphisms at the FOXP1 locus were found to be significantly associated with Barrett esophagus and esophageal adenocarcinoma¹³⁸. 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}.</p> <p>Potential Treatment Strategies: There are no approved therapies available to address alterations in FOXP1.</p>
<p>● KDM5C W983*</p>	<p>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 cues¹⁴². 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 suppressor¹⁴³. Germline inactivating mutations in KDM5C cause an X-linked intellectual disability syndrome also characterized by short stature and hyperreflexia¹⁴⁴.</p> <p>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 prognosis¹⁴⁹.</p> <p>Potential Treatment Strategies: There are no targeted therapies available to address genomic alterations in KDM5C.</p>

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GENE
ALTERATION

INTERPRETATION

● **LRP1B**

loss exons 6-14

Gene and Alteration: LRP1B encodes the low-density lipoprotein receptor-related protein 1B, also called LRPDIT. LRP1B 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^{50,150,151}. The LRP1B 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 LRP1B 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 growth¹⁵². In addition, heterozygous mice that express a C-terminally truncated LRP1B missing codons 3547- 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 inviable¹⁵³. Therefore, it is possible that truncated proteins are still functional.

Frequency and Prognosis: LRP1B mutations have been frequently reported in many types of cancer, including 12-16% of multiple myeloma^{154,155}, 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, LRP1B 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). LRP1B is commonly inactivated in non- small cell lung cancer cell lines, and low expression of LRP1B mRNA was associated with poor patient outcome^{156,157,158}.

Potential Treatment Strategies: There are no therapies or clinical trials that address the loss or mutation of LRP1B in cancer. In some tumor types, such as high-grade serous cancer (HGSC), LRP1B deletion has been reported to be associated with resistance to liposomal doxorubicin¹⁵⁹.

● **SPTA1**Q1346fs*3, splice
site 3570-2A>T

Gene and Alteration: SPTA1 encodes the protein spectrin alpha chain 1, a component of the cytoskeleton of erythrocytes¹⁶⁰. Germline mutations in SPTA1 have been associated with disorders featuring abnormally shaped erythrocytes, such as elliptocytosis and spherocytosis¹⁶¹.

Frequency and Prognosis: SPTA1 mutations have been found in 9% of glioblastoma samples analyzed in one study¹⁶², 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.

● **TP53**

I255S

Gene and Alteration: Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers¹⁶³. 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^{164,165,166,167}. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers^{168,169,170,171,172,173}. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹⁷⁴ to 1:20,000¹⁷³, and in the appropriate clinical context, germline testing of TP53 is recommended.

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GENE ALTERATION	INTERPRETATION
	<p>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)^{2,175,176,177,178} and specifically in 45% of lung adenocarcinoma samples^{179,180}. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma¹⁸¹.</p> <p>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^{182,183,184,185}, therapies that reactivate mutant p53 such as APR-246¹⁸⁶, or p53 gene therapy and immunotherapeutics such as SGT-53^{187,188,189,190} 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 disease¹⁹¹. 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 xenotransplant mouse model¹⁹². 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 under way for some tumor types for patients with a TP53 mutation.</p>

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THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY

SUMMARY OF DATA IN PATIENT TUMOR TYPE

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 specifically¹⁹⁶. 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 afatinib¹⁹⁷. 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 NSCLC²² and 9/14 patients with T790M-positive NSCLC²⁰². 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 adenocarcinoma²⁰³. The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease²⁰⁵, including T790M-positive cases^{205,206}, although adverse reactions may be a concern with this combination²⁰⁷. Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel²⁰⁸.

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 cancer⁴⁶, or melanoma (Johnson et al., 2016; ASCO Abstract 105) and case reports in endometrial cancer^{53,54} and glioblastoma⁵⁵, 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 efficacy^{212,213}. 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-naïve 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)³⁸, colorectal cancer⁴⁶, or melanoma (Johnson et al., 2016; ASCO Abstract 105) and case reports in endometrial cancer^{53,54} 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-naïve 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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ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Ado-trastuzumab emtansine	<p>Approved Indications: 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.</p> <p>Gene Association: ERBB2 activating mutations or amplification may predict sensitivity to T-DM1.</p> <p>Supporting Data: A patient with non-small cell lung cancer, disease progression on two prior lines of chemotherapy, and an activating ERBB2 alteration (exon 20 insertion) experienced a rapid and durable response to T-DM1^{221,222}. The vast majority of data on the therapeutic use of T-DM1 has been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy²²³. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane^{14,224}. Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively^{225,226}.</p>
Lapatinib	<p>Approved Indications: Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.</p> <p>Gene Association: 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 trastuzumab¹⁸.</p> <p>Supporting Data: Investigations into the efficacy of lapatinib have primarily been in the context of breast cancer. In 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) cells²²⁷. A Phase 1 study of single-agent lapatinib included 9 unselected patients with lung cancer and reported 1 case of prolonged stable disease²²⁸. 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 warranted²²⁹.</p>
Pertuzumab	<p>Approved Indications: 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 cancer¹².</p> <p>Gene Association: ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab.</p>

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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 cancer²³⁰. 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 NSCLC²³¹. In a Phase 2 study of pertuzumab in NSCLC, no responses were observed and the progression-free survival was 6.1 weeks²³². 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)²³³; a reduction in circulating tumor cells was noted and correlated with reduction in tumor size²³⁴. 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 events²³⁵.

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^{11,18}. A patient with HER2-positive parotid salivary duct carcinoma also reported a PR following treatment with trastuzumab in combination with carboplatin and docetaxel²³⁶.

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 immunohistochemistry²³⁷. 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 trastuzumab²³⁸. HER2 expression did not impact the results of this study²³⁸. A patient with lung adenocarcinoma that was HER2-positive by FISH and harbored an ERBB2 G776L mutation experienced a partial response on trastuzumab and paclitaxel⁹. 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 chemotherapy¹¹.

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 carcinoma⁴⁵, 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.

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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)²³⁹. 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 reported²⁴⁰. 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 angiomyolipoma 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^{74,75}. 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 alterations⁸⁴. 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)¹¹⁵.

Supporting Data: A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity²⁴², 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 +/- bevacizumab in advanced NSCLC and found the combinations produced 1 complete response and 10 partial responses (n=52), although treatments were not well tolerated²⁴³. 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^{244,245}. 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 months²⁴⁶. 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 combination⁸³.

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^{74,75}. 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 alterations⁸⁴.

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 point²⁴⁷. 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 disease²⁴⁸.

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.

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CLINICAL TRIALS TO CONSIDER

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE

RATIONALE FOR POTENTIAL CLINICAL TRIALS

ERBB2

amplification -
equivocal

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 using keyword terms such as "ERBB2", "HER2", "trastuzumab", "lapatinib", "pertuzumab", "ado-trastuzumab emtansine", "afatinib", "HSP90", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
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 Nor-MDP Adjuvant in Patients With Advanced Solid Tumors	Phase 1	ERBB2	Ohio	NCT01376505
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.	Phase 2	EGFR, ERBB2, ERBB4	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)	NCT01953926
Targeted Agent and Profiling Utilization Registry (TAPUR) Study	Phase 2	ALK, Others	Michigan, North Carolina	NCT02693535
My Pathway: An Open Label Phase IIa 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	Phase 2	EGFR, ERBB2, BRAF, SMO	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	NCT02091141
Phase I Trial Evaluating Safety and Tolerability of the Irreversible Epidermal Growth Factor Receptor Inhibitor Afatinib (BIBW 2992) in	Phase 1	EGFR, ERBB2, KIT, PDGFRs, SRC, ABL	Florida	NCT01999985

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

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CLINICAL TRIALS TO CONSIDER

GENE

RATIONALE FOR POTENTIAL CLINICAL TRIALS

Tumor Mutation

Burden

TMB-High; 37.53

Muts/Mb

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".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase Ib Study of the Safety and Pharmacology of Atezolizumab (Anti-PD-L1 Antibody) Administered With Bevacizumab and/or With Chemotherapy in Patients With Advanced Solid Tumors	Phase 1	PD-1, VEGFA	Colorado, Connecticut, District of Columbia, Illinois, Massachusetts, New York, North Carolina, Tennessee	NCT01633970
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	Phase 2	PD-1	California, Indiana, Nebraska, New Jersey	NCT02343952
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-Naïve and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer	Phase 3	PD-L1	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)	NCT02657434
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)	Phase 3	PD-1	California, Illinois, Maryland, Massachusetts, New York, North Carolina, South Carolina, Moscow (Russian Federation), North Ryde (Australia)	NCT02775435

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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	PD-1, CTLA4	Alabama, California, Connecticut, Georgia, Kentucky, Maryland, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Washington, multiple ex-US locations	NCT02477826
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	Phase 3	PD-1	Arizona, California, Colorado, Florida, Illinois, Maryland, Nebraska, New York, Ohio, Oregon, South Carolina, Tennessee, Texas, Virginia, Washington, Ontario (Canada)	NCT02713867
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]	Phase 3	PD-L1	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)	NCT02813785

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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".

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

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STK11 loss or inactivating mutations may predict sensitivity to mTOR inhibitors or SRC inhibitors.

STK11

splice site 921-1G>C

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".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I Study of BKM120 and Everolimus in Advanced Solid Malignancies	Phase 1	PI3K, mTOR	Georgia	NCT01470209
A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3K α Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	PI3K-alpha, mTORC1, mTORC2	Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)	NCT01899053
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)	Phase 1	EGFR, ERBB2, KIT, PDGFRs, SRC, ABL	Florida	NCT01999985
Phase I Study of MLN0128 (NSC# 768435) in Combination With Ziv-Aflibercept (NSC# 724770) in Patients With Advanced Cancers	Phase 1	mTORC1, mTORC2	Texas	NCT02159989
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	Phase 1	mTORC1, mTORC2	Florida, Oklahoma, Tennessee	NCT02412722

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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.

AKT3 E115K	ARAF G446D	BTK E215V	CD79B splice site 592-2A>C	CDK12 amplification	CDK8 M273I
CSF1R L471M	EPHA5 N120K	ERBB4 N1029K,splice site 3136-2A>T	FLT4 E1002K	GLI1 R1068G	GNAS P98L
GPR124 Q227K,V688L	HSD3B1 V224_V226>G*CV, Y225C	IL7R H309Q	KEAP1 E488K	LRP1B D3844H,G4366W	MDM2 G137C
Microsatellite status MS-Stable	MLL2 Q3738H	MLL3 C388F	NOTCH1 G661S	NTRK3 H632N	PIK3CG L838M
PRDM1 amplification	PRKDC E2175Q,rearrangement	RUNX1T1 D477Y,V16L	SLIT2 V1290A	SMO V294F	SPOP amplification
WISP3 amplification					

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APPENDIX

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	ATRAX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6	BCOR
BCORL1	BLM	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTB	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	ERF1	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	SOC3	SOX10
SOX2	SOX9	SPEN	SPOP	SPTA1		STAG2	STAT3	STAT4	STK11
SUFU	SYK	TAF1	TBX3	TERC	TERT (promoter only)	TET2	TGFB2	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 Mutation Burden

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FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency $\geq 10\%$	>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 $\geq 20\%$	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 $\geq 30\%$ 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 $\geq 30\%$ 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 $\geq 20\%$ tumor nuclei)**		>90.0% ¹ >99.0% for ALK fusion ² (CI* 89.1%-100%)
Sensitivity: Microsatellite status	At $\geq 20\%$ 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 Mutation Burden	At $\geq 20\%$ 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

** 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

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 assayed 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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- ¹ Higgins MJ, Baselga J (2011) Targeted therapies for breast cancer. *J Clin Invest* 121(10):3797-803.
- ² Cancer Genome Atlas Research Network (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 511(7511):543-50.
- ³ Swanton C, Futreal A, Eisen T (2006) Her2-targeted therapies in non-small cell lung cancer. *Clin Cancer Res* 12(14 Pt 2):4377s-4383s.
- ⁴ Nakamura H, Kawasaki N, Taguchi M, et al. (2005) Association of HER-2 overexpression with prognosis in nonsmall cell lung carcinoma: a metaanalysis. *Cancer* 103(9):1865-73.
- ⁵ Tan D, Deeb G, Wang J, et al. (2003) HER-2/neu protein expression and gene alteration in stage I-IIIa non-small-cell lung cancer: a study of 140 cases using a combination of high throughput tissue microarray, immunohistochemistry, and fluorescent in situ hybridization. *Diagn Mol Pathol* 12(4):201-11.
- ⁶ Slamon DJ, Leyland-Jones B, Shak S, et al. (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344(11):783-92.
- ⁷ Bang YJ, Van Cutsem E, Feyereislova A, et al. (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 376(9742):687-97.
- ⁸ Chumsri S, Weidler J, Ali S, et al. (2015) Prolonged Response to Trastuzumab in a Patient With HER2-Nonamplified Breast Cancer With Elevated HER2 Dimerization Harboring an ERBB2 S310F Mutation. *J Natl Compr Canc Netw* 13(9):1066-70.
- ⁹ Cappuzzo F, Bemis L, Varella-Garcia M (2006) HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. *N Engl J Med* 354(24):2619-21.
- ¹⁰ Falchook GS, Janku F, Tsao AS, et al. (2013) Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. *J Thorac Oncol* 8(2):e19-20.
- ¹¹ Mazières J, Peters S, Lepage B, et al. (2013) Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 31(16):1997-2003.
- ¹² Baselga J, Cortés J, Kim SB, et al. (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 366(2):109-19.
- ¹³ Swain SM, Baselga J, Kim SB, et al. (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 372(8):724-34.
- ¹⁴ Verma S, Miles D, Gianni L, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 367(19):1783-91.
- ¹⁵ Cameron D, Casey M, Oliva C, et al. (2010) Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 15(9):924-34.
- ¹⁶ Geyer CE, Forster J, Lindquist D, et al. (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 355(26):2733-43.
- ¹⁷ Serra V, Vivancos A, Puente XS, et al. (2013) Clinical response to a lapatinib-based therapy for a Li-Fraumeni syndrome patient with a novel HER2V659E mutation. *Cancer Discov* 3(11):1238-44.

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- ¹⁸ Ali SM, Alpaugh RK, Downing SR, et al. (2014) Response of an ERBB2-Mutated Inflammatory Breast Carcinoma to Human Epidermal Growth Factor Receptor 2-Targeted Therapy. J Clin Oncol ePub Feb 2014.
- ¹⁹ Lin NU, Winer EP, Wheatley D, et al. (2012) A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. Breast Cancer Res Treat 133(3):1057-65.
- ²⁰ Schwab CL, Bellone S, English DP, et al. (2014) Afatinib demonstrates remarkable activity against HER2-amplified uterine serous endometrial cancer in vitro and in vivo. Br J Cancer 111(9):1750-6.
- ²¹ De Grève J, Teugels E, Geers C, et al. (2012) Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 76(1):123-7.
- ²² De Grève J, Moran T, Graas MP, et al. (2015) Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma. Lung Cancer 88(1):63-9.
- ²³ Gandhi L, Bahleda R, Tolaney SM, et al. (2014) Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. J Clin Oncol 32(2):68-75.
- ²⁴ Ben-Baruch NE, Bose R, Kavuri SM, et al. (2015) HER2-Mutated Breast Cancer Responds to Treatment With Single-Agent Neratinib, a Second-Generation HER2/EGFR Tyrosine Kinase Inhibitor. J Natl Compr Canc Netw 13(9):1061-4.
- ²⁵ Kris MG, Camidge DR, Giaccone G, et al. (2015) Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol ePub Apr 2015.
- ²⁶ Takada M, Higuchi T, Tozuka K, et al. (2013) Alterations of the genes involved in the PI3K and estrogen-receptor pathways influence outcome in human epidermal growth factor receptor 2-positive and hormone receptor-positive breast cancer patients treated with trastuzumab-containing neoadjuvant chemotherapy. BMC Cancer 13:241.
- ²⁷ Jensen JD, Knoop A, Laenkholm AV, et al. (2012) PIK3CA mutations, PTEN, and pHER2 expression and impact on outcome in HER2-positive early-stage breast cancer patients treated with adjuvant chemotherapy and trastuzumab. Ann Oncol 23(8):2034-42.
- ²⁸ Berns K, Horlings HM, Hennessy BT, et al. (2007) A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. Cancer Cell 12(4):395-402.
- ²⁹ Dave B, Migliaccio I, Gutierrez MC, et al. (2011) Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers. J Clin Oncol 29(2):166-73.
- ³⁰ Loibl S, von Minckwitz G, Schneeweiss A, et al. (2014) PIK3CA Mutations Are Associated With Lower Rates of Pathologic Complete Response to Anti-Human Epidermal Growth Factor Receptor 2 (HER2) Therapy in Primary HER2-Overexpressing Breast Cancer. J Clin Oncol ePub Sep 2014.
- ³¹ Barbareschi M, Cuorvo LV, Girlando S, et al. (2012) PI3KCA mutations and/or PTEN loss in Her2-positive breast carcinomas treated with trastuzumab are not related to resistance to anti-Her2 therapy. Virchows Arch 461(2):129-39.
- ³² Guarneri V, Generali DG, Frassoldati A, et al. (2014) Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. J Clin Oncol 32(10):1050-7.
- ³³ Jones KL, Buzdar AU (2009) Evolving novel anti-HER2 strategies. Lancet Oncol 10(12):1179-87.
- ³⁴ Zagouri F, Sergentanis TN, Chrysikos D, et al. (2013) Hsp90 inhibitors in breast cancer: a systematic review. Breast 22(5):569-78.

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- ³⁵ Pfeifer GP, You YH, Besaratinia A (2005) Mutations induced by ultraviolet light. *Mutat Res* 571(1-2):19-31.
- ³⁶ Hill VK, Gartner JJ, Samuels Y, et al. (2013) The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet* 14:257-79.
- ³⁷ Pfeifer GP, Denissenko MF, Olivier M, et al. (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene* 21(48):7435-51.
- ³⁸ Rizvi NA, Hellmann MD, Snyder A, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 348(6230):124-8.
- ³⁹ Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. (2013) Integrated genomic characterization of endometrial carcinoma. *Nature* 497(7447):67-73.
- ⁴⁰ Briggs S, Tomlinson I (2013) Germline and somatic polymerase ϵ and δ mutations define a new class of hypermutated colorectal and endometrial cancers. *J Pathol* 230(2):148-53.
- ⁴¹ Heitzer E, Tomlinson I (2014) Replicative DNA polymerase mutations in cancer. *Curr Opin Genet Dev* 24:107-13.
- ⁴² Cancer Genome Atlas Network (2012) Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 487(7407):330-7.
- ⁴³ Roberts SA, Gordenin DA (2014) Hypermutation in human cancer genomes: footprints and mechanisms. *Nat Rev Cancer* 14(12):786-800.
- ⁴⁴ Snyder A, Makarov V, Merghoub T, et al. (2014) Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 371(23):2189-99.
- ⁴⁵ Rosenberg JE, Hoffman-Censits J, Powles T, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 387(10031):1909-20.
- ⁴⁶ Le DT, Uram JN, Wang H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* ePub May 2015.
- ⁴⁷ Xiao D, Pan H, Li F, et al. (2016) Analysis of ultra-deep targeted sequencing reveals mutation burden is associated with gender and clinical outcome in lung adenocarcinoma. *Oncotarget* 7(16):22857-64.
- ⁴⁸ Shim HS, Kenudson M, Zheng Z, et al. (2015) Unique Genetic and Survival Characteristics of Invasive Mucinous Adenocarcinoma of the Lung. *J Thorac Oncol* 10(8):1156-62.
- ⁴⁹ Govindan R, Ding L, Griffith M, et al. (2012) Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell* 150(6):1121-34.
- ⁵⁰ Ding L, Getz G, Wheeler DA, et al. (2008) Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 455(7216):1069-75.
- ⁵¹ Imielinski M, Berger AH, Hammerman PS, et al. (2012) Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell* 150(6):1107-20.
- ⁵² Kim Y, Hammerman PS, Kim J, et al. (2014) Integrative and comparative genomic analysis of lung squamous cell carcinomas in East Asian patients. *J Clin Oncol* 32(2):121-8.
- ⁵³ Mehnert JM, Panda A, Zhong H, et al. (2016) Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. *J Clin Invest* 126(6):2334-40.

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- ⁵⁴ Santin AD, Bellone S, Buza N, et al. (2016) Regression of chemotherapy-resistant Polymerase epsilon (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab. Clin Cancer Res ePub Aug 2016.
- ⁵⁵ Bouffet E, Larouche V, Campbell BB, et al. (2016) Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J Clin Oncol ePub Mar 2016.
- ⁵⁶ Van Allen EM, Miao D, Schilling B, et al. (2015) Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 350(6257):207-11.
- ⁵⁷ Curto M, McClatchey AI (2008) Nf2/Merlin: a coordinator of receptor signalling and intercellular contact. Br J Cancer 98(2):256-62.
- ⁵⁸ Manetti ME, Geden S, Bott M, et al. (2012) Stability of the tumor suppressor merlin depends on its ability to bind paxillin LD3 and associate with β 1 integrin and actin at the plasma membrane. Biol Open 1(10):949-57.
- ⁵⁹ Laulajainen M, Melikova M, Muranen T, et al. (2012) Distinct overlapping sequences at the carboxy-terminus of merlin regulate its tumour suppressor and morphogenic activity. J Cell Mol Med 16(9):2161-75.
- ⁶⁰ Lallemand D, Saint-Amaux AL, Giovannini M (2009) Tumor-suppression functions of merlin are independent of its role as an organizer of the actin cytoskeleton in Schwann cells. J Cell Sci 122(Pt 22):4141-9.
- ⁶¹ Sherman L, Xu HM, Geist RT, et al. (1997) Interdomain binding mediates tumor growth suppression by the NF2 gene product. Oncogene 15(20):2505-9.
- ⁶² Li W, Cooper J, Karajannis MA, et al. (2012) Merlin: a tumour suppressor with functions at the cell cortex and in the nucleus. EMBO Rep 13(3):204-15.
- ⁶³ Stokowski RP, Cox DR (2000) Functional analysis of the neurofibromatosis type 2 protein by means of disease-causing point mutations. Am J Hum Genet 66(3):873-91.
- ⁶⁴ Mani T, Hennigan RF, Foster LA, et al. (2011) FERM domain phosphoinositide binding targets merlin to the membrane and is essential for its growth-suppressive function. Mol Cell Biol 31(10):1983-96.
- ⁶⁵ Evans GR, Lloyd SK, Ramsden RT (2011) Neurofibromatosis type 2. Adv Otorhinolaryngol 70:91-8.
- ⁶⁶ Lu-Emerson C, Plotkin SR (2009) The neurofibromatoses. Part 2: NF2 and schwannomatosis. Rev Neurol Dis 6(3):E81-6.
- ⁶⁷ Asthagiri AR, Parry DM, Butman JA, et al. (2009) Neurofibromatosis type 2. Lancet 373(9679):1974-86.
- ⁶⁸ Cancer Genome Atlas Research Network (2012) Comprehensive genomic characterization of squamous cell lung cancers. Nature 489(7417):519-25.
- ⁶⁹ Yoo NJ, Park SW, Lee SH (2012) Mutational analysis of tumour suppressor gene NF2 in common solid cancers and acute leukaemias. Pathology 44(1):29-32.
- ⁷⁰ Iyer G, Hanrahan AJ, Milowsky MI, et al. (2012) Genome sequencing identifies a basis for everolimus sensitivity. Science 338(6104):221.
- ⁷¹ Ganesan P, Moulder S, Lee JJ, et al. (2014) Triple Negative Breast Cancer Patients Treated at MD Anderson Cancer Center in Phase I Trials: Improved Outcomes with Combination Chemotherapy and Targeted Agents. Mol Cancer Ther ePub Sep 2014.
- ⁷² Ali SM, Miller VA, Ross JS, et al. (2015) Exceptional Response on Addition of Everolimus to Taxane in Urothelial Carcinoma Bearing an NF2 Mutation. Eur Urol ePub Jan 2015.

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- ⁷³ Moulder S, Helgason T, Janku F, et al. (2015) Inhibition of the Phosphoinositide 3-kinase Pathway for the Treatment of Patients with Metastatic Metaplastic Breast Cancer. *Ann Oncol* ePub Apr 2015.
- ⁷⁴ López-Lago MA, Okada T, Murillo MM, et al. (2009) Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling. *Mol Cell Biol* 29(15):4235-49.
- 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 meningioma and schwannoma growth. *Mol Cell Biol* 29(15):4250-61.
- ⁷⁶ Poulikakos PI, Xiao GH, Gallagher R, et al. (2006) Re-expression of the tumor suppressor NF2/merlin inhibits invasiveness in mesothelioma cells and negatively regulates FAK. *Oncogene* 25(44):5960-8.
- ⁷⁷ Shapiro IM, Kolev VN, Vidal CM, et al. (2014) Merlin deficiency predicts FAK inhibitor sensitivity: a synthetic lethal relationship. *Sci Transl Med* 6(237):237ra68.
- ⁷⁸ Ammoun S, Cunliffe CH, Allen JC, et al. (2010) ErbB/HER receptor activation and preclinical efficacy of lapatinib in vestibular schwannoma. *Neuro-oncology* 12(8):834-43.
- ⁷⁹ Karajannis MA, Legault G, Hagiwara M, et al. (2012) Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro-oncology* 14(9):1163-70.
- ⁸⁰ Garcia-Rendueles ME, Ricarte-Filho JC, Untch BR, et al. (2015) NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition. *Cancer Discov* ePub Sep 2015.
- ⁸¹ Ammoun S, Flaiz C, Ristic N, et al. (2008) Dissecting and targeting the growth factor-dependent and growth factor-independent extracellular signal-regulated kinase pathway in human schwannoma. *Cancer Res* 68(13):5236-45.
- ⁸² Yi C, Troutman S, Fera D, et al. (2011) A tight junction-associated Merlin-angiomotin complex mediates Merlin's regulation of mitogenic signaling and tumor suppressive functions. *Cancer Cell* 19(4):527-40.
- ⁸³ Tolcher AW, Bendell JC, Papadopoulos KP, et al. (2014) A Phase IB Trial of the Oral MEK Inhibitor Trametinib (GSK1120212) in Combination With Everolimus in Patients With Advanced Solid Tumors. *Ann Oncol* ePub Oct 2014.
- ⁸⁴ Shaw RJ, Bardeesy N, Manning BD, et al. (2004) The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell* 6(1):91-9.
- ⁸⁵ Carretero J, Shimamura T, Rikova K, et al. (2010) Integrative genomic and proteomic analyses identify targets for Lkb1-deficient metastatic lung tumors. *Cancer Cell* 17(6):547-59.
- ⁸⁶ Ollila S, Mäkelä TP (2011) The tumor suppressor kinase LKB1: lessons from mouse models. *J Mol Cell Biol* 3(6):330-40.
- ⁸⁷ Qiu W, Schönleben F, Thaker HM, et al. (2006) A novel mutation of STK11/LKB1 gene leads to the loss of cell growth inhibition in head and neck squamous cell carcinoma. *Oncogene* 25(20):2937-42.
- ⁸⁸ Mehenni H, Gehrig C, Nezu J, et al. (1998) Loss of LKB1 kinase activity in Peutz-Jeghers syndrome, and evidence for allelic and locus heterogeneity. *Am J Hum Genet* 63(6):1641-50.
- ⁸⁹ Karuman P, Gozani O, Odze RD, et al. (2001) The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. *Mol Cell* 7(6):1307-19.
- ⁹⁰ Baas AF, Boudeau J, Sapkota GP, et al. (2003) Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD. *EMBO J* 22(12):3062-72.

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- ⁹¹ Zeng PY, Berger SL (2006) LKB1 is recruited to the p21/WAF1 promoter by p53 to mediate transcriptional activation. *Cancer Res* 66(22):10701-8.
- ⁹² Boudeau J, Scott JW, Resta N, et al. (2004) Analysis of the LKB1-STRAD-MO25 complex. *J Cell Sci* 117(Pt 26):6365-75.
- ⁹³ Scott KD, Nath-Sain S, Agnew MD, et al. (2007) LKB1 catalytically deficient mutants enhance cyclin D1 expression. *Cancer Res* 67(12):5622-7.
- ⁹⁴ Xie Z, Dong Y, Zhang J, et al. (2009) Identification of the serine 307 of LKB1 as a novel phosphorylation site essential for its nucleocytoplasmic transport and endothelial cell angiogenesis. *Mol Cell Biol* 29(13):3582-96.
- ⁹⁵ Boudeau J, Kieloch A, Alessi DR, et al. (2003) Functional analysis of LKB1/STK11 mutants and two aberrant isoforms found in Peutz-Jeghers Syndrome patients. *Hum Mutat* 21(2):172.
- ⁹⁶ Forcet C, Etienne-Manneville S, Gaudé H, et al. (2005) Functional analysis of Peutz-Jeghers mutations reveals that the LKB1 C-terminal region exerts a crucial role in regulating both the AMPK pathway and the cell polarity. *Hum Mol Genet* 14(10):1283-92.
- ⁹⁷ Zhang L, Wang JC, Hou L, et al. (2015) Functional Role of Histidine in the Conserved His-x-Asp Motif in the Catalytic Core of Protein Kinases. *Sci Rep* 5:10115.
- ⁹⁸ Amos CI, Keitheri-Cheteri MB, Sabripour M, et al. (2004) Genotype-phenotype correlations in Peutz-Jeghers syndrome. *J Med Genet* 41(5):327-33.
- ⁹⁹ Hearle N, Schumacher V, Menko FH, et al. (2006) Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 12(10):3209-15.
- ¹⁰⁰ van der Groep P, van der Wall E, van Diest PJ (2011) Pathology of hereditary breast cancer. *Cell Oncol (Dordr)* 34(2):71-88.
- ¹⁰¹ Koivunen JP, Kim J, Lee J, et al. (2008) Mutations in the LKB1 tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. *Br J Cancer* 99(2):245-52.
- ¹⁰² Ji H, Ramsey MR, Hayes DN, et al. (2007) LKB1 modulates lung cancer differentiation and metastasis. *Nature* 448(7155):807-10.
- ¹⁰³ An SJ, Chen ZH, Su J, et al. (2012) Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status. *PLoS ONE* 7(6):e40109.
- ¹⁰⁴ Liu Y, Marks K, Cowley GS, et al. (2013) Metabolic and functional genomic studies identify deoxythymidylate kinase as a target in LKB1-mutant lung cancer. *Cancer Discov* 3(8):870-9.
- ¹⁰⁵ Gao B, Sun Y, Zhang J, et al. (2010) Spectrum of LKB1, EGFR, and KRAS mutations in chinese lung adenocarcinomas. *J Thorac Oncol* 5(8):1130-5.
- ¹⁰⁶ Huang YH, Chen ZK, Huang KT, et al. (2013) Decreased expression of LKB1 correlates with poor prognosis in hepatocellular carcinoma patients undergoing hepatectomy. *Asian Pac J Cancer Prev* 14(3):1985-8.
- ¹⁰⁷ Shen Z, Wen XF, Lan F, et al. (2002) The tumor suppressor gene LKB1 is associated with prognosis in human breast carcinoma. *Clin Cancer Res* 8(7):2085-90.
- ¹⁰⁸ Contreras CM, Gurumurthy S, Haynie JM, et al. (2008) Loss of Lkb1 provokes highly invasive endometrial adenocarcinomas. *Cancer Res* 68(3):759-66.
- ¹⁰⁹ Gurumurthy S, Hezel AF, Sahin E, et al. (2008) LKB1 deficiency sensitizes mice to carcinogen-induced tumorigenesis. *Cancer Res* 68(1):55-63.

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- ¹¹⁰Shackelford DB, Vasquez DS, Corbeil J, et al. (2009) mTOR and HIF-1 α -mediated tumor metabolism in an LKB1 mouse model of Peutz-Jeghers syndrome. *Proc Natl Acad Sci USA* 106(27):11137-42.
- ¹¹¹Baselga J, Campone M, Piccart M, et al. (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 366(6):520-9.
- ¹¹²Hudes G, Carducci M, Tomczak P, et al. (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 356(22):2271-81.
- ¹¹³Fury MG, Sherman E, Haque S, et al. (2012) A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors. *Cancer Chemother Pharmacol* 69(3):591-8.
- ¹¹⁴Moroney J, Fu S, Moulder S, et al. (2012) Phase I study of the antiangiogenic antibody bevacizumab and the mTOR/hypoxia-inducible factor inhibitor temsirolimus combined with liposomal doxorubicin: tolerance and biological activity. *Clin Cancer Res* 18(20):5796-805.
- ¹¹⁵Klumpen HJ, Queiroz KC, Spek CA, et al. (2011) mTOR inhibitor treatment of pancreatic cancer in a patient With Peutz-Jeghers syndrome. *J Clin Oncol* 29(6):e150-3.
- ¹¹⁶Chang BL, Zheng SL, Isaacs SD, et al. (2004) A polymorphism in the CDKN1B gene is associated with increased risk of hereditary prostate cancer. *Cancer Res* 64(6):1997-9.
- ¹¹⁷Cai H, Xiang YB, Qu S, et al. (2011) Association of genetic polymorphisms in cell-cycle control genes and susceptibility to endometrial cancer among Chinese women. *Am J Epidemiol* 173(11):1263-71.
- ¹¹⁸Esteban-Jurado C, Vila-Casadesús M, Garre P, et al. (2014) Whole-exome sequencing identifies rare pathogenic variants in new predisposition genes for familial colorectal cancer. *Genet Med ePub Jul 2014*.
- ¹¹⁹Stephens PJ, Tarpey PS, Davies H, et al. (2012) The landscape of cancer genes and mutational processes in breast cancer. *Nature* 486(7403):400-4.
- ¹²⁰Molatore S, Kiermaier E, Jung CB, et al. (2010) Characterization of a naturally-occurring p27 mutation predisposing to multiple endocrine tumors. *Mol Cancer* 9:116.
- ¹²¹Pellegata NS, Quintanilla-Martinez L, Siggelkow H, et al. (2006) Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci USA* 103(42):15558-63.
- ¹²²Erlanson M, Landberg G (2001) Prognostic implications of p27 and cyclin E protein contents in malignant lymphomas. *Leuk Lymphoma* 40(5-6):461-70.
- ¹²³Filipits M, Pohl G, Stranzl T, et al. (2003) Low p27Kip1 expression is an independent adverse prognostic factor in patients with multiple myeloma. *Clin Cancer Res* 9(2):820-6.
- ¹²⁴Chang H, Jiang N, Jiang H, et al. (2010) CKS1B nuclear expression is inversely correlated with p27Kip1 expression and is predictive of an adverse survival in patients with multiple myeloma. *Haematologica* 95(9):1542-7.
- ¹²⁵Zhan F, Colla S, Wu X, et al. (2007) CKS1B, overexpressed in aggressive disease, regulates multiple myeloma growth and survival through SKP2- and p27Kip1-dependent and -independent mechanisms. *Blood* 109(11):4995-5001.
- ¹²⁶Kullmann MK, Grubbauer C, Goetsch K, et al. (2013) The p27-Skp2 axis mediates glucocorticoid-induced cell cycle arrest in T-lymphoma cells. *Cell Cycle* 12(16):2625-35.

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- ¹²⁷ Koon HB, Ippolito GC, Banham AH, et al. (2007) FOXP1: a potential therapeutic target in cancer. *Expert Opin Ther Targets* 11(7):955-65.
- ¹²⁸ Brown PJ, Ashe SL, Leich E, et al. (2008) Potentially oncogenic B-cell activation-induced smaller isoforms of FOXP1 are highly expressed in the activated B cell-like subtype of DLBCL. *Blood* 111(5):2816-24.
- ¹²⁹ Giatromanolaki A, Koukourakis MI, Sivridis E, et al. (2006) Loss of expression and nuclear/cytoplasmic localization of the FOXP1 forkhead transcription factor are common events in early endometrial cancer: relationship with estrogen receptors and HIF-1alpha expression. *Mod Pathol* 19(1):9-16.
- ¹³⁰ Put N, Deeren D, Michaux L, et al. (2011) FOXP1 and PAX5 are rare but recurrent translocations partners in acute lymphoblastic leukemia. *Cancer Genet* 204(8):462-4.
- ¹³¹ Ernst T, Score J, Deininger M, et al. (2011) Identification of FOXP1 and SNX2 as novel ABL1 fusion partners in acute lymphoblastic leukaemia. *Br J Haematol* 153(1):43-6.
- ¹³² Klampfl T, Harutyunyan A, Berg T, et al. (2011) Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. *Blood* 118(1):167-76.
- ¹³³ Milosevic JD, Puda A, Malcovati L, et al. (2012) Clinical significance of genetic aberrations in secondary acute myeloid leukemia. *Am J Hematol* 87(11):1010-6.
- ¹³⁴ Barrans SL, Fenton JA, Banham A, et al. (2004) Strong expression of FOXP1 identifies a distinct subset of diffuse large B-cell lymphoma (DLBCL) patients with poor outcome. *Blood* 104(9):2933-5.
- ¹³⁵ Wong KK, Gascoyne DM, Brown PJ, et al. (2014) Reciprocal expression of the endocytic protein HIP1R and its repressor FOXP1 predicts outcome in R-CHOP-treated diffuse large B-cell lymphoma patients. *Leukemia* 28(2):362-72.
- ¹³⁶ Goatly A, Bacon CM, Nakamura S, et al. (2008) FOXP1 abnormalities in lymphoma: translocation breakpoint mapping reveals insights into deregulated transcriptional control. *Mod Pathol* 21(7):902-11.
- ¹³⁷ Rouhigharabaei L, Finalet Ferreira J, Tousseyn T, et al. (2014) Non-IG Aberrations of FOXP1 in B-Cell Malignancies Lead to an Aberrant Expression of N-Truncated Isoforms of FOXP1. *PLoS ONE* 9(1):e85851.
- ¹³⁸ Levine DM, Ek WE, Zhang R, et al. (2013) A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. *Nat Genet* 45(12):1487-93.
- ¹³⁹ Fox SB, Brown P, Han C, et al. (2004) Expression of the forkhead transcription factor FOXP1 is associated with estrogen receptor alpha and improved survival in primary human breast carcinomas. *Clin Cancer Res* 10(10):3521-7.
- ¹⁴⁰ Rayoo M, Yan M, Takano EA, et al. (2009) Expression of the forkhead box transcription factor FOXP1 is associated with oestrogen receptor alpha, oestrogen receptor beta and improved survival in familial breast cancers. *J Clin Pathol* 62(10):896-902.
- ¹⁴¹ Feng J, Zhang X, Zhu H, et al. (2012) High expression of FoxP1 is associated with improved survival in patients with non-small cell lung cancer. *Am J Clin Pathol* 138(2):230-5.
- ¹⁴² Mersman DP, Du HN, Fingerman IM, et al. (2009) Polyubiquitination of the demethylase Jhd2 controls histone methylation and gene expression. *Genes Dev* 23(8):951-62.
- ¹⁴³ Kim TD, Shin S, Janknecht R (2008) Repression of Smad3 activity by histone demethylase SMCX/JARID1C. *Biochem Biophys Res Commun* 366(2):563-7.

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- ¹⁴⁴Abidi FE, Holloway L, Moore CA, et al. (2008) Mutations in JARID1C are associated with X-linked mental retardation, short stature and hyperreflexia. *J Med Genet* 45(12):787-93.
- ¹⁴⁵Dagliesh GL, Furge K, Greenman C, et al. (2010) Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. *Nature* 463(7279):360-3.
- ¹⁴⁶Niu X, Zhang T, Liao L, et al. (2012) The von Hippel-Lindau tumor suppressor protein regulates gene expression and tumor growth through histone demethylase JARID1C. *Oncogene* 31(6):776-86.
- ¹⁴⁷Hakimi AA, Chen YB, Wren J, et al. (2013) Clinical and pathologic impact of select chromatin-modulating tumor suppressors in clear cell renal cell carcinoma. *Eur Urol* 63(5):848-54.
- ¹⁴⁸Gossage L, Murtaza M, Slatter AF, et al. (2014) Clinical and pathological impact of VHL, PBRM1, BAP1, SETD2, KDM6A, and JARID1c in clear cell renal cell carcinoma. *Genes Chromosomes Cancer* 53(1):38-51.
- ¹⁴⁹Stein J, Majores M, Rohde M, et al. (2014) KDM5C Is Overexpressed in Prostate Cancer and Is a Prognostic Marker for Prostate-Specific Antigen-Relapse Following Radical Prostatectomy. *Am J Pathol ePub* Jul 2014.
- ¹⁵⁰Smith DI, Zhu Y, McAvoy S, et al. (2006) Common fragile sites, extremely large genes, neural development and cancer. *Cancer Lett* 232(1):48-57.
- ¹⁵¹Nakagawa T, Pimkhaokham A, Suzuki E, et al. (2006) Genetic or epigenetic silencing of low density lipoprotein receptor-related protein 1B expression in oral squamous cell carcinoma. *Cancer Sci* 97(10):1070-4.
- ¹⁵²Liu CX, Ranganathan S, Robinson S, et al. (2007) gamma-Secretase-mediated release of the low density lipoprotein receptor-related protein 1B intracellular domain suppresses anchorage-independent growth of neuroglioma cells. *J Biol Chem* 282(10):7504-11.
- ¹⁵³Dietrich MF, van der Weyden L, Prosser HM, et al. (2010) Ectodomains of the LDL receptor-related proteins LRP1b and LRP4 have anchorage independent functions in vivo. *PLoS ONE* 5(4):e9960.
- ¹⁵⁴Chapman MA, Lawrence MS, Keats JJ, et al. (2011) Initial genome sequencing and analysis of multiple myeloma. *Nature* 471(7339):467-72.
- ¹⁵⁵Leich E, Weißbach S, Klein HU, et al. (2013) Multiple myeloma is affected by multiple and heterogeneous somatic mutations in adhesion- and receptor tyrosine kinase signaling molecules. *Blood Cancer J* 3:e102.
- ¹⁵⁶Liu CX, Musco S, Lisitsina NM, et al. (2000) Genomic organization of a new candidate tumor suppressor gene, LRP1B. *Genomics* 69(2):271-4.
- ¹⁵⁷Liu CX, Musco S, Lisitsina NM, et al. (2000) LRP-DIT, a putative endocytic receptor gene, is frequently inactivated in non-small cell lung cancer cell lines. *Cancer Res* 60(7):1961-7.
- ¹⁵⁸Meng H, Chen G, Zhang X, et al. (2011) Stromal LRP1 in lung adenocarcinoma predicts clinical outcome. *Clin Cancer Res* 17(8):2426-33.
- ¹⁵⁹Cowin PA, George J, Fereday S, et al. (2012) LRP1B deletion in high-grade serous ovarian cancers is associated with acquired chemotherapy resistance to liposomal doxorubicin. *Cancer Res* 72(16):4060-73.
- ¹⁶⁰Zhang R, Zhang C, Zhao Q, et al. (2013) Spectrin: structure, function and disease. *Sci China Life Sci* 56(12):1076-85.
- ¹⁶¹Bogardus H, Schulz VP, Maksimova Y, et al. (2014) Severe nondominant hereditary spherocytosis due to uniparental isodisomy at the SPTA1 locus. *Haematologica ePub* Jun 2014.

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- ¹⁶²Brennan CW, Verhaak RG, McKenna A, et al. (2013) The somatic genomic landscape of glioblastoma. *Cell* 155(2):462-77.
- ¹⁶³Brown CJ, Lain S, Verma CS, et al. (2009) Awakening guardian angels: drugging the p53 pathway. *Nat Rev Cancer* 9(12):862-73.
- ¹⁶⁴Kato S, Han SY, Liu W, et al. (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. *Proc Natl Acad Sci USA* 100(14):8424-9.
- ¹⁶⁵Joerger AC, Fersht AR (2008) Structural biology of the tumor suppressor p53. *Annu Rev Biochem* 77:557-82.
- ¹⁶⁶Kamada R, Nomura T, Anderson CW, et al. (2011) Cancer-associated p53 tetramerization domain mutants: quantitative analysis reveals a low threshold for tumor suppressor inactivation. *J Biol Chem* 286(1):252-8.
- ¹⁶⁷Kim H, Kim K, Choi J, et al. (2012) p53 requires an intact C-terminal domain for DNA binding and transactivation. *J Mol Biol* 415(5):843-54.
- ¹⁶⁸Bougeard G, Renaux-Petel M, Flaman JM, et al. (2015) Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. *J Clin Oncol* 33(21):2345-52.
- ¹⁶⁹Sorrell AD, Espenschied CR, Culver JO, et al. (2013) Tumor protein p53 (TP53) testing and Li-Fraumeni syndrome : current status of clinical applications and future directions. *Mol Diagn Ther* 17(1):31-47.
- ¹⁷⁰Nichols KE, Malkin D, Garber JE, et al. (2001) Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. *Cancer Epidemiol Biomarkers Prev* 10(2):83-7.
- ¹⁷¹Taubert H, Meye A, Würl P (1998) Soft tissue sarcomas and p53 mutations. *Mol Med* 4(6):365-72.
- ¹⁷²Kleihues P, Schäuble B, zur Hausen A, et al. (1997) Tumors associated with p53 germline mutations: a synopsis of 91 families. *Am J Pathol* 150(1):1-13.
- ¹⁷³Gonzalez KD, Noltner KA, Buzin CH, et al. (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Oncol* 27(8):1250-6.
- ¹⁷⁴Laloo F, Varley J, Ellis D, et al. (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. *Lancet* 361(9363):1101-2.
- ¹⁷⁵Mogi A, Kuwano H (2011) TP53 mutations in nonsmall cell lung cancer. *J Biomed Biotechnol* 2011:583929.
- ¹⁷⁶Tekpli X, Landvik NE, Skaug V, et al. (2013) Functional effect of polymorphisms in 15q25 locus on CHRNA5 mRNA, bulky DNA adducts and TP53 mutations. *Int J Cancer* 132(8):1811-20.
- ¹⁷⁷Vignot S, Frampton GM, Soria JC, et al. (2013) Next-generation sequencing reveals high concordance of recurrent somatic alterations between primary tumor and metastases from patients with non-small-cell lung cancer. *J Clin Oncol* 31(17):2167-72.
- ¹⁷⁸Maeng CH, Lee HY, Kim YW, et al. (2013) High-throughput molecular genotyping for small biopsy samples in advanced non-small cell lung cancer patients. *Anticancer Res* 33(11):5127-33.
- ¹⁷⁹Cortot AB, Younes M, Martel-Planche G, et al. (2014) Mutation of TP53 and alteration of p14(arf) expression in EGFR- and KRAS-mutated lung adenocarcinomas. *Clin Lung Cancer* 15(2):124-30.
- ¹⁸⁰Itakura M, Terashima Y, Shingyoji M, et al. (2013) High CC chemokine receptor 7 expression improves postoperative prognosis of lung adenocarcinoma patients. *Br J Cancer* 109(5):1100-8.
- ¹⁸¹Seo JS, Ju YS, Lee WC, et al. (2012) The transcriptional landscape and mutational profile of lung adenocarcinoma. *Genome Res* 22(11):2109-19.

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- ¹⁸² Hirai H, Arai T, Okada M, et al. (2010) MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. *Cancer Biol Ther* 9(7):514-22.
- ¹⁸³ Bridges KA, Hirai H, Buser CA, et al. (2011) MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. *Clin Cancer Res* 17(17):5638-48.
- ¹⁸⁴ Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. (2011) MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. *Clin Cancer Res* 17(9):2799-806.
- ¹⁸⁵ Osman AA, Monroe MM, Ortega Alves MV, et al. (2015) Wee-1 kinase inhibition overcomes cisplatin resistance associated with high-risk TP53 mutations in head and neck cancer through mitotic arrest followed by senescence. *Mol Cancer Ther* 14(2):608-19.
- ¹⁸⁶ Lehmann S, Bykov VJ, Ali D, et al. (2012) Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. *J Clin Oncol* 30(29):3633-9.
- ¹⁸⁷ Xu L, Huang CC, Huang W, et al. (2002) Systemic tumor-targeted gene delivery by anti-transferrin receptor scFv-immunoliposomes. *Mol Cancer Ther* 1(5):337-46.
- ¹⁸⁸ Xu L, Tang WH, Huang CC, et al. (2001) Systemic p53 gene therapy of cancer with immunolipoplexes targeted by anti-transferrin receptor scFv. *Mol Med* 7(10):723-34.
- ¹⁸⁹ Camp ER, Wang C, Little EC, et al. (2013) Transferrin receptor targeting nanomedicine delivering wild-type p53 gene sensitizes pancreatic cancer to gemcitabine therapy. *Cancer Gene Ther* 20(4):222-8.
- ¹⁹⁰ Kim SS, Rait A, Kim E, et al. (2015) A tumor-targeting p53 nanodelivery system limits chemoresistance to temozolomide prolonging survival in a mouse model of glioblastoma multiforme. *Nanomedicine* 11(2):301-11.
- ¹⁹¹ Senzer N, Nemunaitis J, Nemunaitis D, et al. (2013) Phase I study of a systemically delivered p53 nanoparticle in advanced solid tumors. *Mol Ther* 21(5):1096-103.
- ¹⁹² Ma CX, Cai S, Li S, et al. (2012) Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. *J Clin Invest* 122(4):1541-52.
- ¹⁹³ Kwak EL, Shapiro GI, Cohen SM, et al. (2013) Phase 2 trial of afatinib, an ErbB family blocker, in solid tumors genetically screened for target activation. *Cancer* 119(16):3043-51.
- ¹⁹⁴ Sequist LV, Yang JC, Yamamoto N, et al. (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 31(27):3327-34.
- ¹⁹⁵ Wu YL, Zhou C, Hu CP, et al. (2014) Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 15(2):213-22.
- ¹⁹⁶ Yang JC, Wu YL, Schuler M, et al. (2015) Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* ePub Jan 2015.
- ¹⁹⁷ Soria JC, Felip E, Cobo M, et al. (2015) Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* ePub Jul 2015.
- ¹⁹⁸ Miller VA, Hirsh V, Cadranel J, et al. (2012) Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 13(5):528-38.

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- ¹⁹⁹Chen X, Zhu Q, Zhu L, et al. (2013) Clinical perspective of afatinib in non-small cell lung cancer. *Lung Cancer* 81(2):155-61.
- ²⁰⁰Katakami N, Atagi S, Goto K, et al. (2013) LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 31(27):3335-41.
- ²⁰¹Landi L, Tiseo M, Chiari R, et al. (2014) Activity of the EGFR-HER2 Dual Inhibitor Afatinib in EGFR-Mutant Lung Cancer Patients With Acquired Resistance to Reversible EGFR Tyrosine Kinase Inhibitors. *Clin Lung Cancer* 15(6):411-417.e4.
- ²⁰²Yang JC, Sequist LV, Geater SL, et al. (2015) Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* ePub Jun 2015.
- ²⁰³Wu SG, Liu YN, Tsai MF, et al. (2016) The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. *Oncotarget* ePub Feb 2016.
- ²⁰⁴Kim Y, Ko J, Cui Z, et al. (2012) The EGFR T790M mutation in acquired resistance to an irreversible second-generation EGFR inhibitor. *Mol Cancer Ther* 11(3):784-91.
- ²⁰⁵Janjigian YY, Smit EF, Groen HJ, et al. (2014) Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant EGFR-Mutant Lung Cancer with and without T790M Mutations. *Cancer Discov* ePub Jul 2014.
- ²⁰⁶Ribeiro Gomes J, Cruz MR (2015) Combination of afatinib with cetuximab in patients with EGFR-mutant non-small-cell lung cancer resistant to EGFR inhibitors. *Onco Targets Ther* 8:1137-42.
- ²⁰⁷Castellanos EH, Rivera G, Wakelee H, et al. (2015) Overcoming Resistance Without the Risk of Reaction: Use of Afatinib and Panitumumab in Two Cases of Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer With T790M Mutations. *Clin Lung Cancer* ePub Mar 2015.
- ²⁰⁸Schuler M, Yang JC, Park K, et al. (2016) Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. *Ann Oncol* 27(3):417-23.
- ²⁰⁹Gettinger S, Rizvi NA, Chow LQ, et al. (2016) Nivolumab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* ePub Jun 2016.
- ²¹⁰Rizvi NA, Hellmann MD, Brahmer JR, et al. (2016) Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* ePub Jun 2016.
- ²¹¹Borghaei H, Paz-Ares L, Horn L, et al. (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* ePub Sep 2015.
- ²¹²Brahmer J, Reckamp KL, Baas P, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* ePub May 2015.
- ²¹³Rizvi NA, Mazières J, Planchard D, et al. (2015) Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* ePub Feb 2015.
- ²¹⁴Dudnik E, Yust-Katz S, Nechushtan H, et al. (2016) Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases. *Lung Cancer* 98:114-7.
- ²¹⁵Herbst RS, Baas P, Kim DW, et al. (2015) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* ePub Dec 2015.

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- ²¹⁶ Garon EB, Rizvi NA, Hui R, et al. (2015) Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. N Engl J Med ePub Apr 2015.
- ²¹⁷ Goldberg SB, Gettinger SN, Mahajan A, et al. (2016) Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 17(7):976-83.
- ²¹⁸ Junttila TT, Li G, Parsons K, et al. (2011) Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res Treat 128(2):347-56.
- ²¹⁹ Lewis Phillips GD, Li G, Dugger DL, et al. (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 68(22):9280-90.
- ²²⁰ Erickson HK, Park PU, Widdison WC, et al. (2006) Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 66(8):4426-33.
- ²²¹ Weiler D, Diebold J, Strobel K, et al. (2015) Rapid response to trastuzumab emtansine in a patient with HER2-driven lung cancer. J Thorac Oncol 10(4):e16-7.
- ²²² Mazières J, Barlesi F, Filleron T, et al. (2015) Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. Ann Oncol ePub Nov 2015.
- ²²³ Krop IE, Kim SB, González-Martín A, et al. (2014) Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 15(7):689-99.
- ²²⁴ Welslau M, Diéras V, Sohn JH, et al. (2014) Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer 120(5):642-51.
- ²²⁵ Krop IE, LoRusso P, Miller KD, et al. (2012) A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol 30(26):3234-41.
- ²²⁶ Burris HA, Rugo HS, Vukelja SJ, et al. (2011) Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 29(4):398-405.
- ²²⁷ Diaz R, Nguewa PA, Parrondo R, et al. (2010) Antitumor and antiangiogenic effect of the dual EGFR and HER-2 tyrosine kinase inhibitor lapatinib in a lung cancer model. BMC Cancer 10:188.
- ²²⁸ Burris HA, Taylor CW, Jones SF, et al. (2009) A phase I and pharmacokinetic study of oral lapatinib administered once or twice daily in patients with solid malignancies. Clin Cancer Res 15(21):6702-8.
- ²²⁹ Ross HJ, Blumenschein GR, Aisner J, et al. (2010) Randomized phase II multicenter trial of two schedules of lapatinib as first- or second-line monotherapy in patients with advanced or metastatic non-small cell lung cancer. Clin Cancer Res 16(6):1938-49.
- ²³⁰ Agus DB, Gordon MS, Taylor C, et al. (2005) Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol 23(11):2534-43.
- ²³¹ Yamamoto N, Yamada Y, Fujiwara Y, et al. (2009) Phase I and pharmacokinetic study of HER2-targeted rhuMAb 2C4 (Pertuzumab, RO4368451) in Japanese patients with solid tumors. Jpn J Clin Oncol 39(4):260-6.
- ²³² Herbst RS, Davies AM, Natale RB, et al. (2007) Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non small cell lung cancer. Clin Cancer Res 13(20):6175-81.

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- ²³³ Felip E, Ranson M, Cedrés S, et al. (2012) A phase Ib, dose-finding study of erlotinib in combination with a fixed dose of pertuzumab in patients with advanced non-small-cell lung cancer. *Clin Lung Cancer* 13(6):432-41.
- ²³⁴ Punnoose EA, Atwal S, Liu W, et al. (2012) Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. *Clin Cancer Res* 18(8):2391-401.
- ²³⁵ Hughes B, Mileskin L, Townley P, et al. (2014) Pertuzumab and Erlotinib in Patients With Relapsed Non-Small Cell Lung Cancer: A Phase II Study Using 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging. *Oncologist* 19(2):175-6.
- ²³⁶ Wang K, Russell JS, McDermott JD, et al. (2016) Profiling of 149 salivary duct carcinomas, carcinoma ex pleomorphic adenomas, and adenocarcinomas, not otherwise specified reveals actionable genomic alterations. *Clin Cancer Res ePub Jun 2016*.
- ²³⁷ Lara PN, Laptalo L, Longmate J, et al. (2004) Trastuzumab plus docetaxel in HER2/neu-positive non-small-cell lung cancer: a California Cancer Consortium screening and phase II trial. *Clin Lung Cancer* 5(4):231-6.
- ²³⁸ Krug LM, Miller VA, Patel J, et al. (2005) Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced nonsmall cell lung carcinoma. *Cancer* 104(10):2149-55.
- ²³⁹ Fehrenbacher L, Spira A, Ballinger M, et al. (2016) Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 387(10030):1837-46.
- ²⁴⁰ Herbst RS, Soria JC, Kowanetz M, et al. (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 515(7528):563-7.
- ²⁴¹ Hezel AF, Gurumurthy S, Granot Z, et al. (2008) Pancreatic LKB1 deletion leads to acinar polarity defects and cystic neoplasms. *Mol Cell Biol* 28(7):2414-25.
- ²⁴² Soria JC, Shepherd FA, Douillard JY, et al. (2009) Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors. *Ann Oncol* 20(10):1674-81.
- ²⁴³ Eberhardt WE, Mitchell P, Schiller JH, et al. (2014) Feasibility of adding everolimus to carboplatin and paclitaxel, with or without bevacizumab, for treatment-naïve, advanced non-small cell lung cancer. *Invest New Drugs* 32(1):123-34.
- ²⁴⁴ Papadimitrakopoulou VA, Soria JC, Jappe A, et al. (2012) Everolimus and erlotinib as second- or third-line therapy in patients with advanced non-small-cell lung cancer. *J Thorac Oncol* 7(10):1594-601.
- ²⁴⁵ Besse B, Leigh N, Bennouna J, et al. (2014) Phase II study of everolimus-erlotinib in previously treated patients with advanced non-small-cell lung cancer. *Ann Oncol* 25(2):409-15.
- ²⁴⁶ Toffalorio F, Spitaleri G, Catania C, et al. (2014) Phase Ib of sorafenib in combination with everolimus in patients with advanced solid tumors, selected on the basis of molecular targets. *Oncologist* 19(4):344-5.
- ²⁴⁷ Reungwetwattana T, Molina JR, Mandrekar SJ, et al. (2012) Brief report: a phase II "window-of-opportunity" frontline study of the mTOR inhibitor, temsirolimus given as a single agent in patients with advanced NSCLC, an NCCTG study. *J Thorac Oncol* 7(5):919-22.
- ²⁴⁸ Waqar SN, Robinson C, Bradley J, et al. (2014) A phase I study of temsirolimus and thoracic radiation in non--small-cell lung cancer. *Clin Lung Cancer* 15(2):119-23.

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**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.

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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, Ciplastraat 3, 2440 Geel, Belgium.



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