FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
		Breast carcinoma (NOS)

Date of Birth		**Medical Facility**			
Sex	Female	**Ordering Physician**		**Specimen Received**	
FMI Case #		**Additional Recipient**		**Specimen Site**	Lung
Medical Record #		**Medical Facility ID #**		**Date of Collection**	
Specimen ID		**Pathologist**		**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

20 genomic findings

13 therapies associated with potential clinical benefit

0 therapies associated with lack of response

34 clinical trials

TUMOR TYPE: BREAST CARCINOMA (NOS)

Genomic Alterations Identified†

ERBB2 R678Q
PIK3CA H1047R – subclonal# , N1044K, R88Q – subclonal# , V344M – subclonal#
TSC1 L203fs*7
ARID1A splice site 2420-2A>G
ASXL1 G645fs*58
LZTR1 Q10fs*24
MLH1 S446fs*32, V267fs*1
MLL2 A1105fs*14
MSH2 A230fs*16
NOTCH3 A2233fs*9
PPP2R1A R183W – subclonal#
RAD50 N934fs*6
SETD2 R1492*
SMARCA4 R1157W

Additional Findings†

Microsatellite status MSI-High
Tumor Mutation Burden TMB-High; 26 Muts/Mb

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

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
ERBB2 R678Q	Ado-trastuzumab emtansine Lapatinib Neratinib Pertuzumab Trastuzumab	Afatinib	Yes, see clinical trials section

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Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 / CLIA:34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 / CLIA:22D2027531

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Microsatellite status MSI-High	Pembrolizumab	Nivolumab	Yes, see clinical trials section
PIK3CA H1047R - subclonal, N1044K, R88Q - subclonal, V344M - subclonal	Everolimus	Temsirolimus	Yes, see clinical trials section
TSC1 L203fs*7	Everolimus	Temsirolimus	Yes, see clinical trials section
Tumor Mutation Burden TMB-High; 26 Muts/Mb	None	Atezolizumab Avelumab Durvalumab Nivolumab Pembrolizumab	Yes, see clinical trials section
ARID1A splice site 2420-2A>G	None	None	None
ASXL1 G645fs*58	None	None	None
LZTR1 Q10fs*24	None	None	None
MLH1 S446fs*32, V267fs*1	None	None	None
MLL2 A1105fs*14	None	None	None
MSH2 A230fs*16	None	None	None
NOTCH3 A2233fs*9	None	None	None
PPP2R1A R183W - subclonal	None	None	None
RAD50 N934fs*6	None	None	None
SETD2 R1492*	None	None	None
SMARCA4 R1157W	None	None	None

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GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
ERBB2 R678Q	**Gene and Alteration:** ERBB2 (also known as HER2) encodes the receptor tyrosine kinase HER2, which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[1]. The functional effect of ERBB2 R678Q is not clear. Although R678Q had no effect on markers of HER2 activation and was not transforming[2,3], this mutation has been shown to result in upregulation of downstream MAPK signaling[3]. **Frequency and Prognosis:** ERBB2 mutations have been reported in 1-3% of breast invasive carcinoma cases[4,5]. HER2 is predicted to be overexpressed (as assessed by immunohistochemistry, FISH, or CNV analysis) in 12-25% of breast cancers[6,7,8]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[9]. Phosphorylated HER2 (pHER2) was expressed in 62.5% (55/88) of HER2-positive breast cancers, and pHER2 expression was associated with development of trastuzumab resistance[10]. **Potential Treatment Strategies:** On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[11,12,13,14,15,16], pertuzumab in combination with trastuzumab[13,17,18], and ado-trastuzumab emtansine (T-DM1)[19], as well as dual EGFR/HER2 kinase inhibitors such as lapatinib[20,21,22,23], afatinib[16,24,25,26,27], neratinib[28,29], and dacomitinib[30]. 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[31,32,33,34,35]. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alterations is associated with trastuzumab resistance[36] and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib[37]. 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[8,38]. However, as the alteration reported here has not been fully characterized, it is not known if these therapeutic approaches would be relevant.
Microsatellite status MSI-High	**Gene and Alteration:** Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[39]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[39,40,41]. The tumor seen here has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in >30% of microsatellite markers[42,43,44]. MSI-H status indicates high-level deficiency in MMR and typically correlates with loss of expression of at least one, and often two, MMR family proteins[39,41,43,44]. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[39], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[45]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[45,46,47] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[48,49,50]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

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GENE ALTERATION	INTERPRETATION

Frequency and Prognosis: The frequency of MSI in breast cancer varies widely due to difference in patient characteristics and sample sizes in different studies. In a few studies of Lynch syndrome-related breast cancer with small sample sizes (n<10), MSI was observed in 60%-85% of patients[51,52,53,54,55]. However, no MSI was observed in a few larger scale analysis of breast cancer samples[56,57]. Moreover, MSI was reported in 51% of patients with MMR-deficient breast cancer[58]. Furthermore, a prospective study observed increased MSI following chemotherapy treatment, and MSI was associated with incidence of secondary tumors[59].

Potential Treatment Strategies: On the basis of emerging clinical evidence, MSI and associated increased mutational burden[60,61] may predict sensitivity to anti-PD-1 immune checkpoint inhibitors[61,62], including the approved therapies nivolumab (Overman et al., 2016; ASCO Abstract 3501)[63] and pembrolizumab[64,65]. Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-H colorectal cancer (CRC) compared with MSS CRC (40% vs. 0%)[64]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with tumors with high MSI than those without (Overman et al., 2016; ASCO Abstract 3501). An earlier case study reported that nivolumab therapy resulted in a complete response in a patient with MSI-H CRC[63]. In the Phase 1b KEYNOTE-012 trial, of 4 patients with MSI-H gastric cancer, 2 patients reported partial responses, and 2 experienced progressive disease in response to pembrolizumab[66]. The efficacy of immunotherapies in other MSI-H solid tumors is currently under investigation in clinical trials.

● ***PIK3CA***
H1047R - subclonal, N1044K, R88Q - subclonal, V344M - subclonal

Gene and Alteration: PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[67,68]. PIK3CA alterations including those affecting codons R38, R93, G106, K111, E453, E542, E545, Q546, M1043, or H1047, missense mutations R88Q, R108H, R115L, G118D, P124L, N345K, G364R, D350G, E365K, C420R, P449T, P539R, T1025S, or G1049R, and deletions affecting codons 447-455 or delG106_R108, such as observed here, have been characterized as activating and are predicted to be oncogenic[69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84]. The other PIK3CA mutation seen here has not been fully characterized; however, similar alterations have been reported in the context of cancer, which may indicate biological relevance.

Frequency and Prognosis: Mutations in PIK3CA have been reported in 25-40% of breast cancer cases[4,85,86,87,88]. Mutations in exon 20 (H1047R) of PIK3CA have been associated with a better prognosis than mutations occurring in exon 9 (E542K, E545K)[89].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT (Juric et al., 2014; ESMO Abstract 451PD, Banerji et al., 2015; ASCO Abstract 2500)[90]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[91,92,93,94,95,96]. Addition of everolimus to exemestane for the treatment of hormone receptor-positive (HR+)/HER2-negative advanced breast cancer has shown clinical benefit regardless of PIK3CA status[97]. In the BELLE-2 trial for patients with endocrine-resistant HR+ breast cancer, the combination of the pan-PI3K inhibitor buparlisib with fulvestrant resulted in increased progression-free survival (PFS; 7.0 vs. 3.2 months) and overall response rate (ORR; 18% vs. 4%) compared to placebo with fulvestrant in patients with PIK3CA mutation; no significant improvement in PFS or ORR was observed in patients without PIK3CA mutation (Baselga et al., 2015; SABCS Abstract S6-01). PI3K-alpha-selective inhibitors, such as alpelisib, may have a bigger therapeutic window than pan-PI3K inhibitors (Baselga et al., 2015; SABCS Abstract S6-01)[90]. Alpelisib achieved partial responses (PRs) for 11% of patients with PIK3CA-mutated advanced solid tumors (Juric et al., 2014; ESMO Abstract 451PD). For patients with PIK3CA-mutated advanced HR+ breast cancer, hormone therapy combined with alpelisib or taselisib, a PI3K-beta-sparing selective PI3K inhibitor, has shown promising preliminary efficacy, with ORRs of 6-38% (Janku et al., 2014; SABCS Abstract PD5-5, Mayer et al., 2015; AACR Abstract CT232, Saura et al., 2014; SABCS Abstract PD5-2). Furthermore, CDK4/6 inhibitors may sensitize PIK3CA-mutant breast cancers to PI3K inhibitors[98]. A Phase 1 study of the pan-AKT inhibitor AZD5363 observed responses for 3/15 patients with PIK3CA-mutated HR+ breast cancer (Banerji et al., 2015; ASCO Abstract 2500). In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 stable disease)[99]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation[36,92,100,101,102].
● ***TSC1*** L203fs*7	**Gene and Alteration:** TSC1 encodes the protein Hamartin, which interacts with Tuberin, the gene product of TSC2, to inhibit and regulate mTOR activity[103,104]. Any TSC1 alteration that results in disruption of the Hamartin N-terminal domain (amino acids 1-351)[105] or the coiled-coil domain (amino acids 721-997), which participate in oligomerization and interactions with Tuberin[105], is predicted to result in mTOR activation through loss of Hamartin function[105,106,107]. Germline mutations in TSC1 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma[108,109]. Mutations in TSC1 account for approximately 10-30% of reported cases[110]. Prevalence for this disorder in the general population is estimated to be 1:6,000 from birth and a range of 1:12,000 to 1:14,000 in children under 10[111]. Therefore, in the appropriate clinical context, germline testing of TSC1 is recommended. **Frequency and Prognosis:** TSC1 mutations have been reported in 0-1.5% of breast carcinomas[4,5,112,113,114]. One study has reported decreased Hamartin protein expression in invasive breast carcinoma samples, as compared to normal epithelial breast tissue[115]. Decreased Hamartin expression has been associated with poor prognosis in breast cancer patients[115].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Loss or inactivation of TSC1 leads to activation of mTOR and therefore may predict sensitivity to mTOR inhibitors[103,104,116] such as temsirolimus and everolimus. Patients with bladder cancer or RCC harboring TSC1 mutations have been reported to respond to everolimus or temsirolimus, with two reports of complete or partial responses for at least 2 years[117,118,119].
● ***Tumor Mutation Burden*** TMB-High; 26 Muts/Mb	**Gene and Alteration:** Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[120,121] and cigarette smoke in lung cancer[65,122], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[123,124,125,126,127], and microsatellite instability (MSI)[123,126,127]. The tumor seen here harbors a high TMB. This type of mutation load has been shown to be associated with sensitivity to immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[128], anti-PD-L1 therapy in urothelial carcinoma[129], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[64,65], potentially due to expression of immune-reactive neoantigens in these tumors[65]. **Frequency and Prognosis:** Breast carcinoma harbors a median TMB of 3.8 mutations per megabase (muts/Mb), and 3.1% of cases have high TMB (>20 muts/Mb)[130]. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 mutations per megabase (muts/Mb) for luminal A tumors, 1.38 muts/Mb for luminal B tumors, 2.05 muts/Mb for HER2-enriched tumors, and 1.68 muts/Mb for basal-like tumors[4]. In estrogen receptor-positive breast cancer, increased mutation load (> mean of 1.25 muts/Mb) associated with shorter overall survival [hazard ratio (HR) of 2.02] in an analysis of the TCGA data[131]. In another study, the number of mutated genes associated with higher tumor grade[132]. Although the number of mutated genes did not correlate with overall survival by multivariate analysis, cases with 22 or more mutated genes had significantly worse overall survival than cases with fewer than 22 mutated genes (HR of 4.6)[132]. **Potential Treatment Strategies:** On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[128], anti-PD-L1[129,133,134], and anti-PD-1 therapies[64,65,135]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[65]. 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[64,65,135]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[136] or nivolumab[137], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[138], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[139]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[128,140] and anti-PD-1/anti-PD-L1 treatments[133]. 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 muts/Mb)[129], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival[134].

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GENE ALTERATION	INTERPRETATION

● *ARID1A*
splice site 2420-2A>G

Gene and Alteration: ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, which is a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[141,142,143,144,145,146,147,148,149]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[144,145,148,150,151]. ARID1A missense mutations are mostly uncharacterized, whereas several in-frame insertions or deletions, such as Q1334_R1335insQ and A343_A348>A, have been shown to impair ARID1A tumor suppressor activity without affecting ARID1A protein levels[152].

Frequency and Prognosis: ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-57%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (36%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma (CRC), and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2017)[145,153,154,155,156,157]. Low ARID1A expression has been associated with advanced tumor stage in breast carcinoma, although studies are conflicted over the role of ARID1A loss as an independent predictor of overall survival[146,158,159]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[160,161,162,163], CRC[164,165,166], and gastric cancer[147,151,167,168,169].

Potential Treatment Strategies: There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to inhibitors of EZH2[170,171], which are under investigation in clinical trials. Other studies have reported that loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[172,173,174]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy in patients with ovarian clear cell carcinoma[175,176] and to 5-fluorouracil (5-FU) in CRC cell lines[177].

● *ASXL1*
G645fs*58

Gene and Alteration: ASXL1 (additional sex combs-like 1) encodes a chromatin-binding protein involved in transcriptional regulation through interaction with the polycomb complex proteins and various other transcriptional regulators[178,179]. Germline inactivating mutations affecting ASXL1 underlie the very rare developmental disorder Bohring-Opitz syndrome[180]. ASXL1 alterations that remove the PHD domain (amino acids 1491-1541), including truncating mutations and deletions, lead to aberrant epigenetic regulation[179,181,182].

Frequency and Prognosis: ASXL1 mutations have been reported in various solid tumors, including 4% of colorectal cancers[183], 3% of breast cancers[113], 2% of hepatocellular carcinomas[184], 2% (1/61) of prostate cancers[185], and 1.4% (1/74) of head and neck squamous cell carcinomas[186]. ASXL1 amplification has also been reported in 5.1% of cervical cancers[187]. ASXL1 mutations have mainly been studied and reported in the context of hematological malignancies, where they have been correlated with poor prognosis in myelodysplastic syndromes, chronic myelomonocytic leukemia, acute myeloid leukemia, and myeloproliferative neoplasms[178,181,188]. Mutations in ASXL1 have also been associated with clonal hematopoiesis of indeterminate potential (CHIP) in hematologic malignancies[189,190,191,192,193]; however, the role of ASXL1 alterations in solid tumors is unclear.

Potential Treatment Strategies: There are no targeted therapies available to address genomic alterations in ASXL1.

GENE ALTERATION	INTERPRETATION
● ***LZTR1*** Q10fs*24	**Gene and Alteration:** LZTR1 encodes leucine-zipper-like transcription regulator 1, a BTB-Kelch family protein that exclusively localizes to the Golgi network[194]. Germline deletions of LZTR1 may be associated with DiGeorge syndrome, an autosomal-dominant disorder characterized by craniofacial, thymic, parathyroid, and cardiac defects[195,196]. Additionally, germline loss-of-function mutations in LZTR1 are associated with an autosomal dominant inherited disorder of multiple schwannomas[197]. **Frequency and Prognosis:** LZTR1 mutations or deletions have been reported in 4.4% and 22% of glioblastomas (GBM), respectively[198]. This study showed that LZTR1 normally interacts with the Cullin-3 (Cul3) ubiquitin ligase complex and can inhibit the proliferation and self-renewal of GBM cells in sphere culture. Inactivating, GBM-associated mutations in LZTR1 inhibit both its interaction with Cul3 and its anti-proliferative functions[198]. **Potential Treatment Strategies:** There are no targeted therapies approved or in clinical trials that address LZTR1 alterations.
● ***MLH1*** S446fs*32, V267fs*1	**Gene and Alteration:** MLH1 encodes the protein MutL homolog 1, colon cancer, nonpolyposis type 2, which binds PMS2 to form MutLalpha, a complex involved in DNA mismatch repair (MMR)[199]. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[40]. MLH1 alterations that result in disruption or loss of the N-terminal ATPase-containing domain (amino acids 25-336)[200,201,202], the exonuclease 1 (EXO1) interacting region or the C-terminal region necessary for PMS2 binding and formation of the MutL-alpha complex[203], such as observed here, are predicted to be inactivating. Germline mutations in MLH1 are associated with a condition known as Lynch syndrome, which is characterized by increased risk of a number of cancers[45]. Approximately 50% of Lynch syndrome-associated mutations have been attributed to alterations in MLH1[204]. Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) accounts for 1-7% of all colorectal cancers and has an estimated prevalence in the general population between 1:600 and 1:2000[48,49,50]. In the appropriate clinical context, germline testing of MLH1 is recommended. **Frequency and Prognosis:** MLH1 mutation or loss has been reported in each fewer than 1% of breast carcinoma cases in the TCGA datasets[4,114]. One study reported loss of MLH1 protein expression in 1.3% (3/226) of triple-negative breast carcinomas and one of these had MLH1 promoter hypermethylation[205]. Additionally, MLH1 promoter methylation has been reported to be associated with microsatellite instability in urothelial cancers[206]. **Potential Treatment Strategies:** MLH1 inactivation leads to MMR defects, high MSI, and increased mutational burden[44,126,207,208], which may predict response to the FDA-approved anti-PD-1 immunotherapies pembrolizumab and nivolumab[63,64,65]. In a Phase 2 study of MSI-high colorectal cancer (CRC), three patients with MLH1 (germline) mutations experienced one partial response and two stable diseases[64]. Pembrolizumab demonstrated a significantly higher objective response rate in MSI-high CRC compared with microsatellite stable CRC (40% vs. 0%)[64] and its efficacy correlated with high mutational burden in non-small cell lung cancer[65]. Nivolumab achieved a complete response in a patient with MSI-high CRC[63]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[62], potential biomarkers of response to anti-PD-1 immunotherapies. These therapies are in clinical trials for various tumor types and may be appropriate particularly for hypermutant tumors.

GENE ALTERATION	INTERPRETATION
MLL2 A1105fs*14	**Gene and Alteration:** MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[209]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[210]. **Frequency and Prognosis:** Somatic alterations of MLL2 are frequently observed in lymphoma, including in the majority of follicular lymphomas, where the observed pattern of genomic alterations suggests a tumor suppressor function[211]. MLL2 alterations are also observed in a number of solid tumor contexts (COSMIC, 2017), being especially prevalent in squamous cell lung carcinoma[212]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in MLL2.
MSH2 A230fs*16	**Gene and Alteration:** MSH2 encodes a DNA mismatch repair protein belonging to the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[40]. MSH2 alterations that may result in loss or disruption of the EXO1 interaction domain (amino acids 601-671), the MutS core domain (aa 303-645), or the nucleotide triphosphate hydrolase domain (aa 619-855), such as observed here, are predicted to be inactivating[213,214,215,216,217,218,219,220,221,222,223,224,225]. Germline mutations of MMR proteins such as MLH1, MSH2, MSH6, or PMS2 are associated with a condition known as Lynch syndrome, which may lead to nonpolyposis colon cancer, gastric cancer, small bowel, or endometrial cancer[45]. In one large study of Lynch syndrome, endometrial cancer was the most common cancer reported outside the colon, with an incidence of 13.8%[46]. For family members of patients with newly diagnosed endometrial cancer, the clinical utility of testing the patient for germline mutations in MMR genes is higher for mutations in MLH1 or MSH2 than it is for MSH6 or PMS2 mutations[226]. Therefore, in the appropriate clinical context, germline testing of MSH2 is recommended. **Frequency and Prognosis:** In the Breast Invasive Carcinoma TCGA dataset, MSH2 mutation has been observed in approximately 0.5% of cases[4]. MSH2 mutation has been identified in 3.1% (1/32) of breast tumors in one study[227]. Decreased MSH2 protein expression has been reported in 28% (9/32) of breast carcinoma samples and has been associated with microsatellite instability (MSI)[227]. Low MSH2 protein expression has been associated with increased overall and disease-free survival in other cancer types, such as prostate cancer and urothelial carcinoma[228,229,230]. **Potential Treatment Strategies:** MSH2 inactivation leads to MMR defects, MSI, and high mutational burden[231,232,233,234,235], which may predict response to the FDA-approved anti-PD-1 immunotherapies pembrolizumab and nivolumab[63,64,65]. In a Phase 2 study of MSI-high cancers, six patients with MSH2 (germline) mutations reported one partial response and two stable diseases [64]. Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-high CRC compared with microsatellite stable CRC (40% vs. 0%) [64] and its efficacy correlated with high mutational burden in non-small cell lung cancer[65]. Treatment with nivolumab resulted in a complete response in a patient with MSI-high CRC[63]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[62], potential biomarkers of response to PD-1 targeted immunotherapies. These therapies are in clinical trials for various tumor types and may be appropriate particularly in hypermutant tumors. Preclinical studies have shown that tumor cells deficient in MSH2 are markedly sensitive to methotrexate in vitro[236]. Low levels of MSH2 have been observed by immunohistochemistry (IHC) in NSCLC and may predict benefit to cisplatin-based adjuvant chemotherapy[237,238].

GENE ALTERATION	INTERPRETATION

● *NOTCH3*
A2233fs*9

Gene and Alteration: NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[239,240]. Alterations that preserve the ANK repeat region and disrupt or remove the PEST domain have been reported to increase activity of NOTCH1 and NOTCH2[241,242,243,244]. Similar mutations, such as observed here, have been reported in cancer[245] and are likely to also be activating.

Frequency and Prognosis: In the TCGA dataset, NOTCH3 mutation was observed in fewer than 1% of invasive breast carcinoma cases[4]. NOTCH3 amplification and/or overexpression has been reported in fewer than 3% of breast carcinomas with amplification not always correlating with overexpression[246,247,248]. However, in another study, NOTCH3 expression was noted in 9/34 (26.5%) HER2-negative breast cancers compared to 0/14 HER2-positive tumors[249]. In cell-based and xenograft breast cancer models, NOTCH3 signaling has been reported to facilitate cell proliferation, invasion, and tumor growth[247,250,251,252].

Potential Treatment Strategies: Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as OMP-59R5[253], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[250,254,255]. A Phase 1b study of OMP-59R5 in combination with gemcitabine and nab-paclitaxel has shown promising efficacy (up to 50% partial response) in patients with untreated metastatic pancreatic cancer (O'Reilly et al., 2015; Gastrointestinal Cancers Symposium Abstract 278). A Phase 1b study of OMP-59R5 in combination with etoposide and cisplatin for small cell lung cancer reported a median progression free survival of 124 days and 84% overall response rate (Pietanza et al., 2015; ASCO Abstract 7508). The GSI BMS-906024 inhibits NOTCH activity in vitro and exhibits anti-tumor activity in xenograft models of leukemia and triple negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression[256]. These agents are being investigated in preclinical studies and early clinical trials in various tumor types[257].

● *PPP2R1A*
R183W - subclonal

Gene and Alteration: PPP2R1A encodes a regulatory subunit of protein phosphatase 2 (PP2A), which is involved in regulation of the cell cycle transition from mitosis to interphase[258]. A spatially constrained pattern of somatic missense alterations in PPP2R1A, clustered around codons 179, 182, and 256 has been documented[259,260,261,262,263]. Although the functional consequences of these PPP2R1A alterations have not been clearly characterized, they are presumed to disrupt binding of the PP2A regulatory and catalytic subunits, dysregulating normal PP2A function and cell cycle progression[261].

Frequency and Prognosis: PPP2R1A mutations have been reported in several subtypes of ovarian and uterine carcinoma, most frequently in uterine serous carcinoma (up to 33%) (COSMIC, 2017). In addition, concurrent mutations in PPP2R1A, PIK3CA, and TP53 have been reported in cases of uterine serous carcinoma, and were also found in associated serous endometrial intraepithelial carcinomas, suggesting the alterations arose early in the pre-invasive stage of the disease[263]. PPP2R1A mutations have been reported in 9/42 carcinosarcoma samples analyzed[259].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: There are no targeted therapies available to directly address genomic alterations in PPP2R1A. Activation of PP2A with forskolin or the sphingosine analogue FTY720 has be shown to be beneficial in the context of CML and ALL[264], and is being investigated in solid tumors of the lung, breast, and colon[265,266,267]. In addition, other agents have been shown to upregulate PP2A activity in the context of various tumors[268]. However, the efficacy of these compounds in the context of PPP2R1A mutations has not yet been evaluated (PubMed, 2017).
● ***RAD50*** N934fs*6	**Gene and Alteration:** RAD50 binds to MRE11 and NBS1 to form the MRE-RAD50-NBS1 (MRN) complex. The MRN complex regulates DNA double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiotic recombination[269]. RAD50 contains three critical regions that are primarily responsible for its function: the central coiled-coil domain (amino acids 228-1079), the zinc-hook loop (amino acids 635-734), and an ATPase domain formed by portions from both the N and C termini (amino acids 1-45 and 1201-1238). Mutations truncating the RAD50 coiled-coil domain have been shown to negatively impact homologous recombination and nonhomologous end-joining and to inhibit telomere maintenance and meiotic double-strand break (DSB) formation[270]. **Frequency and Prognosis:** RAD50 is mutated at a relatively high frequency in colorectal and endometrial cancers (2-7%) and at lower frequencies across a range of solid tumors (cBioPortal, COSMIC, 2017). Germline mutations in RAD50 have been reported in hereditary breast and/or ovarian cancer (HBOC), but they are rare and not significantly associated with increased risk of cancer[271,272]. High expression of MRE11 or NBS1 protein or the entire MRN complex was shown to be associated with microsatellite stability, earlier tumor stage, and longer survival in patients with colorectal cancer (CRC)[273]. **Potential Treatment Strategies:** There are no targeted therapies approved or in clinical trials that directly address genomic alterations in RAD50. Deficiencies in or disruption of MRN complex components have been shown to sensitize cancer cells to PARP inhibitors, including those under investigation in clinical trials[274,275,276,277,278]. However, conflicting results have been reported regarding whether depletion of RAD50 specifically confers sensitivity to PARP inhibitors[275,277]. In a preclinical study, CRC cells with mutations in both MRE11 and RAD50 were highly sensitive to irinotecan[279], and other studies have reported that disruption of RAD50 sensitizes human cancer cells to cisplatin[280,281]. Furthermore, a case report described a patient with metastatic small cell carcinoma who was treated with a combination of irinotecan and a CHK1/2 inhibitor and achieved a durable complete response that has continued more than 3 years after discontinuation of drug therapy; the study showed that the patient's tumor harbored a destabilizing RAD50 mutation and that RAD50 loss or inactivation moderately sensitizes cells to topoisomerase I inhibitors and provides far stronger sensitivity to such agents in the setting of ATR or CHK1 inactivation[282].
● ***SETD2*** R1492*	**Gene and Alteration:** SETD2 encodes a histone lysine-36 methyltransferase[283] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[284]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[285].

GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[286]. SETD2 mutations have been detected in 6-12% of acute lymphoblastic leukemias (ALL) and reportedly increase chromosomal abnormalities and contribute to leukemia development[287,288,289]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in SETD2.
● ***SMARCA4*** R1157W	**Gene and Alteration:** SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[290]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[291]. The alteration observed here has not been functionally characterized and its effect on SMARCA4 function is unknown, although similar alterations have been seen in the context of cancer, which may indicate biological relevance. **Frequency and Prognosis:** SMARCA4 mutations have been reported in 1.2-1.9% of breast invasive carcinoma cases[4,5,113,114]. One study reported that increased expression of BRG1 associated with inferior overall and disease-free survival in patients with breast cancer[292]. Reduction of BRG1 expression in breast cancer cells inhibits their proliferation[292,293,294]. The role of SMARCA4/BRG1 in cancer is unclear; increased expression has been correlated with advanced stage in prostate cancer and melanoma, however inactivation of BRG1 has been reported in several other types of cancer[295,296,297,298]. **Potential Treatment Strategies:** There are no therapies that directly address mutant SMARCA4 or loss of functional BRG1. However, on the basis of both clinical (Italiano et al., 2015; ECC Abstract 302, Penebre et al., 2015; EORTC Abstract C87) and preclinical (Penebre et al., 2015; EORTC Abstract C87)[171] data, patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with inhibitors of EZH2. In preclinical studies, cells with dual inactivation of SMARCA4 and SMARCA2, which is characteristic of SCCOHT[299,300], were sensitive to EZH2 inhibitors (Penebre et al., 2015; EORTC Abstract C87)[171], and two patients with SCCOHT experienced clinical benefit (1 partial response, 1 long-term stable disease) upon treatment with the EZH2 inhibitor tazemetostat (Italiano et al., 2015; ECC Abstract 302, Penebre et al., 2015; EORTC Abstract C87). Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[301]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[302]. However, because this alteration has not been characterized, it is not known if these therapeutic strategies would be relevant.

THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Ado-trastuzumab emtansine	**Approved Indications:** Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling[303,304]; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[304,305]. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy. **Gene Association:** ERBB2-activating mutation or amplification may predict sensitivity to T-DM1. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant. **Supporting Data:** Although a Phase 2 study reported improved median progression-free survival (PFS) for patients with HER2+ advanced breast cancer treated in the first line with T-DM1 as compared with trastuzumab plus docetaxel (14.2 months vs. 9.2 months, hazard ratio of 0.59)[306], the Phase 3 MARIANNE study reported no significant differences in overall response rate (ORR; 60%, 64%, and 68%) or median PFS (14.1, 15.2, and 13.7 months) when comparing T-DM1 combined with placebo, T-DM1 with pertuzumab, and trastuzumab with taxane, respectively, in this same setting[307]. For patients with HER2+ breast cancer previously treated with HER2-directed therapies, Phase 3 trials of single-agent T-DM1 have reported significant increases in median PFS as compared with physician's choice of therapy (6.2 vs. 3.3 months)[308] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[19,309,310]. These results are comparable to previous Phase 2 studies in patients with HER2+ metastatic breast cancer (MBC) previously treated with HER2-directed therapies with or without chemotherapy[311,312]; although another Phase 2 study reported a lower response rate for T-DM1 after trastuzumab and pertuzumab, one-third of patients received therapy for more than 6 months, thereby suggesting some clinical benefit[313]. Treatment of MBC with T-DM1 in combination with docetaxel was reported to achieve an ORR of 80% and median PFS of 13.8 months[314]. A similar study of T-DM1 combined with paclitaxel and pertuzumab reported an ORR of 52.4%[315]. Patients with newly diagnosed HER2+ locally advanced breast cancer treated with T-DM1 plus docetaxel and with or without pertuzumab achieved pathologic complete response rates of 60.6% and 60.0%, respectively[314]. A Phase 1 study of T-DM1 in combination with the PI3K-alpha inhibitor alpelisib for patients with HER2+ MBC reported a median PFS of 5.6 and 9.8 months for those with or without prior T-DM1 monotherapy treatment (Jain et al., 2016; ASCO Abstract 588). Patients with HER2+ MBC and active central nervous system (CNS) metastases treated with T-DM1 achieved an ORR of 40% (4/10); there was no significant difference in OS between patients with and without CNS metastases (McCabe et al., 2016; ASCO Abstract 582). A retrospective study of patients with breast cancer and brain metastases treated with T-DM1, chemotherapy, and radiotherapy reported 44% (17/39) partial responses, 15% (6/39) stable disease, and a median PFS of 6.1 months[316].
Lapatinib	**Approved Indications:** Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2 (HER2/NEU), and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole to treat HER2-overexpressing (HER2+) metastatic breast cancer. **Gene Association:** ERBB2 activating mutation or amplification may confer sensitivity to lapatinib. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant.

Supporting Data: Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents, and these combination regimens have been shown to extend progression-free survival (PFS) and reduce metastases, as well as to extend overall survival (OS) in some instances[20,21,317,318,319,320]. As first-line therapy for HER2+ metastatic breast cancer, lapatinib plus taxane resulted in shorter median PFS compared with trastuzumab plus taxane (9.0 vs. 11.3 months, hazard ratio of 1.37)[321]. For patients who have progressed on trastuzumab plus taxane, ado-trastuzumab emtansine (T-DM1) was superior to lapatinib plus capecitabine (OS of 30.9 vs. 25.1 months)[19]. Addition of lapatinib to capecitabine had improved PFS compared with capecitabine monotherapy (8.4 vs. 4.4 months) in this setting[21]. Lapatinib plus capecitabine has been reported to reduce the number of newly developed brain metastases[317] and to be active against existing brain metastases (objective central nervous system [CNS] response rate of 66% [29/44])[322]. However, the incidence of CNS metastases was not significantly different with lapatinib plus capecitabine versus trastuzumab plus capecitabine (3% vs. 5%)[323], and CNS disease progression rates were similar for treatment with T-DM1 and with lapatinib plus capecitabine[324]. Phase 2 and 3 trials comparing the efficacy of lapatinib and trastuzumab for the treatment of HER2+ breast cancer in the neoadjuvant setting reported conflicting results, with the combination of lapatinib and trastuzumab generally achieving slightly higher response rates[318,319,320]. A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported 3-year event-free survival rates of 78%, 76%, and 84%, with 3-year OS rates of 93%, 90%, and 95%, respectively[325]. In a Phase 3 study for patients with early HER2+ breast cancer, adjuvant lapatinib (alone, in sequence, or in combination with trastuzumab) did not significantly improve disease-free survival (DFS) and added toxicity compared with adjuvant trastuzumab[326]. Adjuvant lapatinib also did not significantly extend DFS in a placebo-controlled Phase 3 study[327]. In postmenopausal patients with hormone receptor-positive (HR+) HER2+ metastatic breast cancer, lapatinib combined with letrozole increased median PFS compared to letrozole alone (8.2 vs. 3.0 months)[328]. Addition of lapatinib to fulvestrant did not improve outcome for patients with advanced HR+ advanced breast cancer and prior aromatase inhibitor therapy (median PFS of 4.7 vs. 3.8 months), although lapatinib associated with longer median PFS for HER2+ patients in this trial (5.9 vs. 3.3 months)[329]. As neoadjuvant therapy for HR+ HER2-negative breast cancer, lapatinib combined with letrozole did not significantly improve response rates, but showed a trend toward a higher response rate for patients with PIK3CA-mutant tumors[37]. Four patients with HER3-positive and HER2-negative newly diagnosed breast cancer had clinical responses to neoadjuvant lapatinib[330].

Neratinib

Approved Indications: Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early stage HER2-positive breast cancer following adjuvant trastuzumab.

Gene Association: On the basis of extensive clinical (Hyman et al., 2016; San Antonio Breast Cancer Symposium Abstract PD2-08)[29,331,332,333] and preclinical[2,334,335,336,337] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant.

Supporting Data: In a Phase 3 study of patients with HER2-positive, early stage breast cancer previously treated with trastuzumab, neratinib significantly improved the two-year invasive disease-free survival compared to placebo (94.2% vs. 91.9%; HR=0.67, p=0.0091)[332]. In Phase 2 trials of patients with ERBB2-mutated, non-amplified, metastatic breast cancer, a clinical benefit rate (CBR) of 31-42% and median progression-free survival (PFS) of 3.5-4 months were achieved with neratinib (Hyman et al., 2016; San Antonio Breast Cancer Symposium Abstract PD2-08)[331]. For patients with advanced HER2-positive breast cancer, neratinib treatment resulted in PFS of 22.3 weeks for patients with prior trastuzumab treatment and of 39.6 weeks for those with no prior trastuzumab treatment[338]. In patients with breast cancer and HER2-positive brain metastases treated with neratinib, the CNS objective response rate (ORR) was 8% (3/40)[339]. The therapeutic efficacy of neratinib in combination with other targeted or chemotherapies is also under investigation. Preliminary data from a Phase 2 trial of patients with ERBB2-mutated, ER-positive metastatic breast cancer treated with neratinib plus fulvestrant reported an ORR of 55% (including 2 CRs and 4PRs)(Hyman et al., 2016; San Antonio Breast Cancer Symposium Abstract PD2-08). In a Phase 2 study of neratinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, the ORR was 63%[340]. In this population, PFS with neratinib treatment was 4.5 months as compared to 6.8 months with lapatinib plus capecitabine[341]. Neratinib plus paclitaxel for patients with HER2-positive metastatic breast cancer resulted in an ORR of 73%[342]. In this population, neratinib and vinorelbine for previously treated patients resulted in a higher ORR in patients who were lapatinib-naive (41%) as compared to those patients who had prior lapatinib (8%)[343]. In a Phase 1 study of neratinib with trastuzumab and paclitaxel for patients with HER2-positive metastatic breast cancer, an ORR of 38% and a CBR of 52% was reported[344]. As first-line therapy in HER2-positive metastatic breast cancer, PFS or ORR did not significantly differ with neratinib plus paclitaxel compared to trastuzumab plus paclitaxel; however, patients treated with neratinib had a lower incidence of CNS recurrences[345]. As neoadjuvant treatment in HER2-positive, hormone-receptor negative breast cancer, the pathologic complete response rate was 56% with neratinib plus paclitaxel as compared to 33% with trastuzumab plus paclitaxel[333].

Pertuzumab

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 cancer[17].

Gene Association: ERBB2 activating mutation or amplification may predict sensitivity to pertuzumab. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant.

Supporting Data: A Phase 3 randomized trial in patients with HER2+ metastatic breast cancer (MBC) treated with first-line trastuzumab and docetaxel demonstrated a significant improvement in progression-free survival (PFS; 12.4 vs. 18.7 months) and in median overall survival (OS; 40.8 vs. 56.5 months) with addition of pertuzumab compared with placebo[17,18,346]. A Phase 2 study in patients with locally advanced breast cancer (LABC) or early stage HER2+ breast cancer treated with various combinations of pertuzumab, trastuzumab, and docetaxel reported the greatest benefit when using neoadjuvant pertuzumab combined with trastuzumab and docetaxel (5-year PFS rate of 84)[347,348]. A study of pertuzumab combined with paclitaxel and ado-trastuzumab emtansine reported an overall response rate of 52.4% in patients with previously treated HER2+ MBC or LABC[315]. In a Phase 3 study of patients with HER2+ MBC failing on first-line trastuzumab, addition of pertuzumab to trastuzumab and capecitabine was reported to increase median PFS (11.1 vs. 9.0 months) and OS (36.1 vs. 28.1 months) when compared with trastuzumab plus capecitabine (Urruticoechea et al., 2016; ASCO Abstract 504). A trial of 12 patients with HER2+ MBC progressing on pertuzumab plus trastuzumab were reported to have 1 complete response (CR), 1 partial response (PR), and 5 stable diseases (SD) after treatment with a combination of pertuzumab, trastuzumab, and gemcitabine (Iyengar et al., 2016; ASCO Abstract 611). A Phase 1 trial of salvage therapy with a combination of pertuzumab, trastuzumab, and gemcitabine for 6 patients with HER2+ MBC after progression on trastuzumab reported 1 PR, 4 SD, 1 progressive disease, and a median PFS of 3.8 months (Soliman et al., 2016; ASCO Abstract 595).

Trastuzumab

Approved Indications: Trastuzumab is a monoclonal antibody that targets the protein HER2/NEU (encoded by ERBB2). It is FDA approved for the treatment of HER2-overexpressing breast and metastatic gastric or gastroesophageal adenocarcinomas.

Gene Association: ERBB2 activating mutation or amplification may confer sensitivity to trastuzumab. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant.

Supporting Data: Trastuzumab has been approved for breast cancer based on a Phase 3 randomized clinical trial comparing treatment with trastuzumab and chemotherapy to treatment with chemotherapy alone, which showed that the addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, response duration, and overall survival[11]. A subsequent Phase 3 study of patients with HER2-positive (HER2+) breast cancer reported 5-year event-free survival in 58% of patients treated with trastuzumab plus neoadjuvant therapy, compared to 43% in patients treated with neoadjuvant therapy alone[349]. Long-term follow-up Phase 2 analysis reported a 5-year distant disease-free survival rate of 92% in patients with HER2+ breast cancer treated with dose-dense chemotherapy and trastuzumab and 89% in patients treated with lapatinib and dose-dense chemotherapy[350]. In one study of patients with early breast cancer treated with neoadjuvant trastuzumab, higher ERBB2 copy number (HER2/CEP17 ratio >6) correlated with increased incidence of pathologic complete response compared to lower ERBB2 copy number[351]. A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported 3-year event-free survival rates of 78%, 76%, and 84%, and 3-year overall survival rates of 93%, 90%, and 95%, respectively[325]. Trastuzumab is also approved in combination with pertuzumab and docetaxel for the first-line treatment of metastatic HER2+ breast cancer[17,346]. Two Phase 3 studies have evaluated whether addition of the mTOR inhibitor everolimus would circumvent or overcome resistance of HER2-positive breast cancer to trastuzumab-based therapy: As first-line treatment for patients with HER2-positive breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median progression-free survival (PFS) in the full study population (15.0 months with everolimus vs. 14.5 months with placebo) but increased PFS in the hormone receptor-negative subpopulation by 7.2 months (20.3 months vs. 13.1 months)[352]. For patients with trastuzumab-resistant HER2-positive breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months)[353]. Follow-up exploratory analysis of these studies showed that patients with PIK3CA alterations achieved extended median PFS with everolimus compared with placebo (hazard ratio [HR] = 0.69), when combined with trastuzumab plus paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months)[92]. Low PTEN expression or PTEN loss also significantly associated with benefit from added everolimus in the combined analysis of both studies (HR = 0.50) (Slamon et al., 2015; ASCO Abstract 512)[353].

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 as second-line treatment for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma; recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy; adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy; and advanced urothelial carcinoma that is not eligible for cisplatin-containing chemotherapy, has progressed on or after platinum chemotherapy, or has progressed within 12 months of neoadjuvant or adjuvant platinum chemotherapy. Pembrolizumab is approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, and as first-line treatment in combination with pemetrexed and carboplatin for metastatic nonsquamous NSCLC.

Gene Association: On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various microsatellite instability (MSI)-high or mismatch repair-deficient solid tumors (Ayers et al., 2016; ASCO-SITC Abstract P60, Diaz et al., 2016; ASCO Abstract 3003, Le et al., 2016; ASCO GI Abstract 195, Fader et al., 2016; SGO Abstract 3)[64], MSI may predict sensitivity to pembrolizumab. On the basis of emerging clinical data in patients with non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017)[65], colorectal cancer[64], or melanoma[133] and case reports in endometrial cancer[136,137] and glioblastoma[139], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

Supporting Data: In a Phase 1b study of pembrolizumab for patients with PD-L1-positive triple-negative breast cancer, an overall response rate of 18.5% (5/27) was achieved and tumor shrinkage was observed in 37.5% (9/24) of patients; one patient (3.7%, 1/27) had a complete response, 14.8% (4/27) of patients had a partial response, and 25.9% (7/27) of patients had stable disease; responses were durable (range, 15 to more than 47 weeks) and the 12-month overall survival rate was 43.1%[354].

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: On the basis of extensive clinical[91,92,95] and preclinical[96] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus. Loss or inactivation of TSC1 may result in mTOR activation and predict sensitivity to mTOR inhibitors such as everolimus. In several clinical studies, patients with bladder cancer, renal cell carcinoma (RCC), or collision tumor with TSC1 mutation or TSC1 partial homozygous deletion have been reported to respond to everolimus or temsirolimus, with two reports of complete or partial responses for at least 2 years[117,118,119,355]. TSC1 or TSC2 mutations were identified in 21% (9/43) of patients with renal cell carcinoma that responded to everolimus or temsirolimus, compared to 6% (2/36) of nonresponders[356].

Supporting Data: In the BOLERO-2 Phase 3 study, addition of everolimus to exemestane as second-line therapy for hormone receptor-positive (HR+), HER2-negative breast cancer was shown to improve median progression-free survival (PFS) compared to exemestane alone (11.5 vs. 4.1 months) and showed a trend to longer overall survival (31.0 vs. 26.6 months)[357,358,359]; analysis of cell-free DNA revealed a similar benefit with mutant or wild-type PIK3CA [hazard ratio (HR) = 0.37 vs. 0.43][97]. Clinical studies for patients with HR+ breast cancer indicate that everolimus may potentiate letrozole or tamoxifen efficacy and can be safely combined with anastrozole[360,361,362]. Two Phase 3 trials have evaluated whether addition of everolimus would circumvent or overcome resistance of HER2-positive (HER2+) breast cancer to trastuzumab-based therapy: As first-line treatment for patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo) but increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months)[352]. For patients with trastuzumab-resistant HER2+ breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months)[353]. Follow-up exploratory analysis showed that patients with PIK3CA alterations achieved longer median PFS with everolimus vs. placebo (HR = 0.69), when combined with trastuzumab plus paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months)(Slamon et al., 2015; ASCO Abstract 512). Low PTEN expression or PTEN loss also was significantly associated with benefit from added everolimus in the combined analysis of both studies (HR = 0.50), whereas PIK3CA mutation was significantly associated with benefit in HR-negative (HR = 0.43) but not HR+ disease (HR = 0.93) (Slamon et al., 2015; ASCO Abstract 512)[92]. For patients with metastatic triple-negative breast cancer, everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[363]. A Phase 1b trial of a combination of everolimus and the MEK inhibitor trametinib in patients with solid tumors reported frequent adverse events, and the study was unable to identify a recommended Phase 2 dose and schedule for the combination[364].

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER 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 to treat 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. A Phase 2 clinical trial of afatinib in HER2-positive metastatic breast carcinoma reported a 46% clinical benefit rate[24]. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant.

Supporting Data: In a Phase 3 study for patients with HER2-positive (HER2+) breast cancer and disease progression on trastuzumab, afatinib plus vinorelbine compared to trastuzumab plus vinrorelbine did not improve median progression-free survival (5.5 vs. 5.6 months) or objective response rate (ORR) (46% vs. 47%), associated with shorter median overall survival (OS) (20.5 vs. 28.6 months), and was less well tolerated[365]. Afatinib monotherapy achieved an ORR of 11% (4/35) and a median OS of 61 weeks in this setting[24]. For patients with progressive brain metastases after HER2-targeted therapy, treatment with afatinib alone, afatinib combined with vinorelbine, or investigator's choice did not increase patient benefit (12/40 vs. 13/38 vs. 18/43) and caused frequent adverse events[366]. As neoadjuvant treatment for HER2+ breast cancer, afatinib demonstrated a comparable or higher ORR (80%, 8/10) than lapatinib (75%, 6/8) or trastuzumab (36%, 4/11); however, adverse events were more frequent than with lapatinib or trastuzumab[367]. In contrast, a Phase 2 trial reported no objective responses for genomically unselected patients with HER2-negative breast cancer[368]. Afatinib plus letrozole achieved stable disease for 54% (15/28) of patients with estrogen receptor-positive breast cancer who had progressed on single-agent letrozole[369].

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 metastatic non-small cell lung cancer (NSCLC) following disease progression on prior treatments, advanced renal cell carcinoma after prior antiangiogenic therapy, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy, 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 showing strong efficacy of nivolumab for patients with microsatellite instability (MSI)-high colorectal cancer (CRC) (Overman et al., 2016; ASCO Abstract 3501)[63] and additional clinical data predicting association between MSI and markers of response to anti-PD-1 therapy[60,61,62], MSI-high tumors may be sensitive to nivolumab. On the basis of emerging clinical data in patients with non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017)[65], colorectal cancer[64], or melanoma[133] and case reports in endometrial cancer[136,137] and glioblastoma[139], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as nivolumab.

Supporting Data: Nivolumab has primarily been investigated in the context of melanoma[370,371,372,373,374], non-small cell lung carcinoma (NSCLC) (Brahmer et al., 2014; ASCO Abstract 8112, Gettinger et al., 2014; ASCO Abstract 8024, Antonia et al., 2014; ASCO Abstract 8023, Rizvi et al., 2014; ASCO Abstract 8022, Antonia et al., 2014; ASCO Abstract 8113)[375,376] and renal cell carcinoma (RCC) (Amin et al., 2014; ASCO Abstract 5010, McDermott et al., 2016, ASCO Abstract 4507)[377,378,379,380]. In a Phase 3 study for patients with platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), nivolumab compared with investigator's choice (methotrexate, docetaxel, or cetuximab) improved median OS (7.5 vs. 5.1 months) and significantly reduced the risk of death (hazard ratio [HR] of 0.70) (Gillison et al., 2016; AACR Abstract CT099, Ferris et al., 2016; ASCO Abstract 6009). Increased survival benefit was observed for patients whose tumors were positive for PD-L1 expression (HR=0.55) or human papillomavirus (HPV) (HR=0.56), although nivolumab also showed efficacy for PD-L1-negative (HR=0.89) or HPV-negative (HR=0.73) patients (Gillison et al., 2016; AACR Abstract CT099). Nivolumab has also achieved clinical benefit in various other cancers, including ovarian cancer (ORR, 6-15%)[381,382], small cell lung cancer (ORR, 18%) (Calvo et al., 2015; ECC Abstract 3098), Hodgkin lymphoma (ORR 87%) (Ansell et al.,2015; ASH Abstract 583)[383], advanced/metastatic gastroesophageal carcinoma (ORR 12-18%) (Le et al., 2016; ASCO GI Cancers Abstract 06, Kojima et al., 2016; ASCO GI Cancers Abstract TPS175), recurrent/progressive glioblastoma (GBM; 12-month OS, 40%) (Reardon et al., 2016; ASCO Abstract 2014), pediatric GBM associated with biallelic mismatch repair deficiency (2/2 partial responses)[139], and hepatocellular carcinoma (ORR, 16%) (Sangro et al., 2016; ASCO Abstract 4078; El-Khoueiry et al., 2016; ASCO Abstract 4012). Nivolumab alone or in combination with pazopanib for previously treated metastatic sarcoma achieved clinical benefit in 39% (9/23) of cases (Paoluzzi et al., 2016; ASCO Abstract 11047); however, another study reported responses in 0% (0/12) of patients with uterine leiomyosarcoma (George et al., 2016; ASCO Abstract 11007). Nivolumab alone or in combination with ipilimumab (at two different dose combinations) for previously treated advanced gastric cancer achieved ORRs of 14% and 10-26%, respectively (Janjigian et al., 2016; ASCO Abstract 4010). Nivolumab in combination with ipilimumab for patients with recurrent bevacizumab-naive GBM achieved stable disease in 43% (13/30) of cases, but with a greater incidence of serious treatment-related adverse events than nivolumab alone (Reardon et al., 2016; ASCO Abstract 2014). Nivolumab and stereotactic radiation have been successfully combined for the treatment of melanoma brain metastases[384].

Temsirolimus

Approved Indications: Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma.

Gene Association: On the basis of extensive clinical[93,94,385] and preclinical[96] evidence, PIK3CA activation may predict sensitivity to mTOR inhibitors such as temsirolimus. In two studies of temsirolimus-containing treatment regimens in a variety of cancer types, response rates of 4/16 (25%)[93] and 7/23 (30%)[385] were reported in patients with PIK3CA-mutant tumors. Loss or inactivation of TSC1 may result in mTOR activation and predict sensitivity to mTOR inhibitors such as temsirolimus. In several clinical studies, patients with bladder cancer, renal cell carcinoma (RCC), or collision tumor with TSC1 mutation or TSC1 partial homozygous deletion have been reported to respond to everolimus or temsirolimus, with two reports of complete or partial responses for at least 2 years[117,118,119,355]. TSC1 or TSC2 mutations were identified in 21% (9/43) of patients with RCC who responded to everolimus or temsirolimus, compared to 6% (2/36) of nonresponders[356].

Supporting Data: A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a complete response (1.4%), partial response (18.9%), or stable disease (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a complete or partial response (36%) or stable disease (16%)[386]. Another Phase 1 trial including patients with several types of cancer reported a 42% incidence of complete or partial responses in patients with metastatic breast cancer[387]. However, a Phase 2 study of temsirolimus in pretreated patients with metastatic breast cancer reported minimal clinical activity and no association with PTEN protein or PIK3CA mutation status[388]. A Phase 3 placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer was terminated at the second interim since the addition of temsirolimus to letrozole did not improve progression-free survival as a first-line therapy[389]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 complete responses, 4 partial responses, 2 instances of stable disease longer than 6 months, and 4 instances of stable disease shorter than 6 months[94].

Atezolizumab

Approved Indications: Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy or who progress during or following platinum-based chemotherapy and to treat patients with metastatic non-small cell lung cancer (NSCLC) and disease progression on prior treatments.

Gene Association: On the basis of emerging clinical data in patients with urothelial carcinoma[129], non-small cell lung cancer (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017), or melanoma[133], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-L1 therapies such as atezolizumab.

Supporting Data: A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 42% (10/24) of patients; no dose-limiting toxicities were observed (Adams et al., 2016; ASCO Abstract 1009). A Phase 3 trial is investigating the efficacy of this combination therapy as first-line treatment for mTNBC (NCT02425891). Atezolizumab has been studied primarily for the treatment of non-small cell lung cancer (NSCLC)[390,391] and urothelial carcinoma[129,392]. An overall response rate of 21% (36/175) was reported in response to atezolizumab for patients with multiple solid tumor types, including NSCLC (12/53), renal cell carcinoma (8/56), melanoma (13/30), and other tumor types (3/23) such as head and neck squamous cell carcinoma, gastric cancer, colorectal carcinoma, and pancreatic cancer[393].

Avelumab

Approved Indications: Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with metastatic Merkel cell carcinoma and patients with advanced urothelial carcinoma who have progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

Gene Association: On the basis of emerging clinical data in patients with urothelial carcinoma[129], non-small cell lung cancer (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017), or melanoma[133], high tumor mutation burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab.

Supporting Data: In metastatic breast cancer, an unconfirmed objective response rate of 5.4% (9/168) and a disease control rate of 29.2% (49/168) were reported for avelumab monotherapy; partial response was seen in 8.8% (5/57) of triple-negative patients (Dirix et al., 2016; SABCS Abstract S1-04).

Durvalumab

Approved Indications: Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

Gene Association: On the basis of emerging clinical data in patients with urothelial carcinoma[129], non-small cell lung cancer (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017), or melanoma[133], high tumor mutational burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as durvalumab.

Supporting Data: Single-agent durvalumab has demonstrated efficacy in urothelial carcinoma (Powles et al., 2017; ASCO Genitourinary Abstract 286)[394], non-small cell lung cancer (Bais et al., 2017; AACR Abstract 3720/5, Garassino et al., 2016; IASLC Abstract PLO4a.03), and head and neck squamous cell carcinoma (Segal et al., 2016; ESMO Abstract 949O, Segal et al., 2015; ASCO Abstract 3011). In patients with advanced solid tumors, durvalumab monotherapy has elicited disease control rates (DCRs) of 36-46% (7/19 to 12/26) in Phase 1/2 studies (Lutzky et al., 2014; ASCO Abstract 3001, Iguchi et al., 2015; ASCO Abstract 3039). Durvalumab is also under investigation in combination with other agents in Phase 1/2 trials. In advanced melanoma, durvalumab in combination with trametinib and dabrafenib elicited objective response rates (ORRs) and DCRs of 76% (16/21) and 100% (21/21) in patients with BRAF-mutant tumors, and durvalumab with trametinib elicited ORRs and DCRs of 21% (3/14) and 64% (9/14) in patients whose tumors were BRAF wild-type (Ribas et al., 2015; ASCO Abstract 3003). Durvalumab in combination with the PARP inhibitor olaparib has shown activity in patients with metastatic castration-resistant prostate cancer and progression on enzalutamide and/or abiraterone (Karzai et al., 2017; ASCO Genitourinary Abstract 162) and in patients with BRCA-wild-type breast or gynecological cancer (Lee et al., 2016; ASCO Abstract 3015). Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680 (Hamid et al., 2016; ESMO Abstract 1050PD), the CXCR2 antagonist AZD5069 (Hong et al., 2016; ESMO 2016 Abstract 1049PD), or the ATR inhibitor AZD6738 (Yap et al., 2016; EORTC-NCI-AACR Abstract 1LBA). In patients with treatment-refractory solid tumors, concurrent durvalumab and radiotherapy achieved an ORR of 60% (6/10) for in-field evaluable lesions, including 2 complete and 4 partial responses[395].

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 as second-line treatment for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma; recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy; adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy; and advanced urothelial carcinoma that is not eligible for cisplatin-containing chemotherapy, has progressed on or after platinum chemotherapy, or has progressed within 12 months of neoadjuvant or adjuvant platinum chemotherapy. Pembrolizumab is approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, and as first-line treatment in combination with pemetrexed and carboplatin for metastatic nonsquamous NSCLC. **Gene Association:** On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various microsatellite instability (MSI)-high or mismatch repair-deficient solid tumors (Ayers et al., 2016; ASCO-SITC Abstract P60, Diaz et al., 2016; ASCO Abstract 3003, Le et al., 2016; ASCO GI Abstract 195, Fader et al., 2016; SGO Abstract 3)[64], MSI may predict sensitivity to pembrolizumab. On the basis of emerging clinical data in patients with non-small cell lung cancer (Spigel et al., 2016; ASCO Abstract 9017)[65], colorectal cancer[64], or melanoma[133] and case reports in endometrial cancer[136,137] and glioblastoma[139], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab. **Supporting Data:** In a Phase 1b study of pembrolizumab for patients with PD-L1-positive triple-negative breast cancer, an overall response rate of 18.5% (5/27) was achieved and tumor shrinkage was observed in 37.5% (9/24) of patients; one patient (3.7%, 1/27) had a complete response, 14.8% (4/27) of patients had a partial response, and 25.9% (7/27) of patients had stable disease; responses were durable (range, 15 to more than 47 weeks) and the 12-month overall survival rate was 43.1%[354].

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: Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months.

While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not 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*** R678Q	ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies and may enhance the efficacy of chemotherapy or therapies targeting other proteins, such as HSP90. However, because this alteration has not been confirmed as activating, it is not clear that this therapeutic strategy would be relevant. 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", "breast carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients With HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment	Phase 3	ERBB2	Alabama, Arizona, California, Colorado, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Mississippi, Missouri, New Hampshire, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Tennessee, Texas, Utah, Virginia, Washington, multiple ex-US locations	NCT02492711
A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting	Phase 3	EGFR, ERBB2, ERBB4	Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Nebraska, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Vermont, multiple ex-US locations	NCT01808573

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CLINICAL TRIALS TO CONSIDER

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
Microsatellite status MSI-High	High microsatellite instability (MSI) and mutational burden, which may predict response to anti-PD-1 immunotherapies. 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 "MSI", "PD-1", "pembrolizumab", "nivolumab", "breast carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
MK-3475 (Pembrolizumab) in Combination With an Anthracycline or Anti-estrogen Therapy in Patients With Triple Negative and Hormone Receptor Positive (HR+ HER2-) Metastatic Breast Cancer	Phase 2	PD-1, Aromatase	California	NCT02648477
A First-in-Human Study of Repeat Dosing With REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death - 1 (PD 1), as Single Therapy and in Combination With Other Anti-Cancer Therapies in Patients With Advanced Malignancies	Phase 1	PD-1	Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Indiana, Kansas, Massachusetts, Michigan, Missouri, Nebraska, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, Tennessee, Texas, Washington, Barcelona (Spain), Madrid (Spain), Melbourne (Australia)	NCT02383212
A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer - (KEYNOTE-355)	Phase 3	PD-1	California, Colorado, Florida, Georgia, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Michigan, Montana, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, South Carolina, South Dakota, Tennessee, Utah, Virginia, Washington, multiple ex-US locations	NCT02819518
A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination With Nivolumab in Advanced/Metastatic Solid Tumors and B-cell Non-Hodgkins Lymphoma	Phase 1/Phase 2	PD-1, 4-1BB	California, Florida, Illinois, Maryland, Massachusetts, New York, Pennsylvania, Texas, Besancon (France), Essen (Germany), Marseille (France), Pamplona (Spain), Rennes Cedex 9 (France), Villejuif (France)	NCT02253992

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CLINICAL TRIALS TO CONSIDER

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
PIK3CA H1047R - subclonal, N1044K, R88Q - subclonal, V344M - subclonal	PIK3CA activating mutations or amplification may predict sensitivity to inhibitors of PI3K, AKT, and/or mTOR. 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 "PI3K", "AKT", "mTOR", "everolimus", "temsirolimus", "breast carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine Therapy +/- One Year of Everolimus in Patients With High-Risk, Hormone Receptor-Positive and HER2/Neu Negative Breast Cancer	Phase 3	Aromatase, ER, LHRH, mTOR	Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming, multiple ex-US locations	NCT01674140
A Phase III Randomized Double-blind, Placebo Controlled Study of Alpelisib in Combination With Fulvestrant for Men and Postmenopausal Women With Hormone Receptor Positive, HER2-negative Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment	Phase 3	ER, PI3K-alpha	Arizona, Arkansas, California, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Missouri, Nebraska, New York, North Carolina, Ohio, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Virginia, Washington, multiple ex-US locations	NCT02437318

CLINICAL TRIALS TO CONSIDER

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***TSC1*** L203fs*7	Loss or inactivation of Hamartin (encoded by TSC1) may lead to increased mTOR activation. Therefore, mTOR inhibitors may be relevant in a tumor with TSC1 loss or mutation. 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", "everolimus", "temsirolimus", "breast carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine Therapy +/- One Year of Everolimus in Patients With High-Risk, Hormone Receptor-Positive and HER2/Neu Negative Breast Cancer	Phase 3	Aromatase, ER, LHRH, mTOR	Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming, multiple ex-US locations	NCT01674140
A Phase I/II, Single Arm, Open-label Study of Ribociclib in Combination With Everolimus + Exemestane in the Treatment of Men and Postmenopausal Women With HR+, HER2- Locally Advanced or Metastatic Breast Cancer Following Progression on a CDK 4/6 Inhibitor	Phase 1/Phase 2	Aromatase, CDK4, CDK6, mTOR	Arizona, Arkansas, California, Connecticut, Florida, Georgia, Indiana, Kansas, Massachusetts, Michigan, Missouri, New Jersey, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Washington	NCT02732119
A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2- Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant	Phase 2	Aromatase, ER, mTORC1, mTORC2	California, Colorado, Florida, Kansas, Maryland, Michigan, Minnesota, New York, Ohio, Tennessee, Texas, Virginia, West Virginia, Antwerpen (Belgium), Bruxelles (Belgium), Calvados (France), Charleroi (Belgium), Libramont	NCT02049957

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CLINICAL TRIALS TO CONSIDER

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
Tumor Mutation Burden TMB-High; 26 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", "breast cancer", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination With MEDI4736 and MEDI0680 Monotherapy in Subjects With Select Advanced Malignancies	Phase 1 / Phase 2	PD-1, PD-L1	Oklahoma, Oregon, South Carolina, Kansas, Kentucky, Minnesota, New Hampshire, New Jersey, Pennsylvania, Washington, West Virginia, New York, California, Ohio, Florida	NCT02118337
A Phase III, Multicenter, Randomized Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab Paclitaxel Compared With Placebo With Nab Paclitaxel for Patients With Previously Untreated Metastatic Triple Negative Breast Cancer	Phase 3	PD-L1	Arkansas, District of Columbia, Maryland, South Carolina, Virginia, Adana (Turkey), Athens (Greece), Avignon (France), Barcelona (Spain), Besancon (France), Bruxelles (Belgium), Gyeonggi-do (Korea, Republic of), Heraklion (Greece), Istanbul (Turkey), Ivanovo (Russian Federation), Izmir (Turkey), Kortrijk (Belgium), Lyon (France), Madrid (Spain), Malaga (Spain), Montpellier (France), Moscow (Russian Federation), New South Wales (Australia), Patras (Greece), Queensland (Australia), Saitama (Japan), Seoul (Korea, Republic of), Sheffield (United Kingdom), Strasbourg (France), Sıhhiye, ANKARA (Turkey), Taichung (Taiwan), Thessaloniki (Greece), Valencia (Spain)	NCT02425891

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.

BRCA2 K607T	***CRLF2*** Q90L	***CYLD*** R19Q	***EPHA5*** N81fs*24	***EPHB1*** K578fs*14	***ERG*** G459D, P416L
ESR1 H6Y	***FANCD2*** R119H	***FANCG*** A576T	***FAT1*** A4419T	***GATA3*** R69M	***GATA6*** T581M
GPR124 R595C	***IKBKE*** R127W	***KDM5A*** G1200fs*9	***KDR*** Q1222R	***KEL*** R516Q	***KIT*** N655K
LRP1B R499W	***MED12*** D1669N	***MLL2*** A1105P, T4193M	***MLL3*** L1315S	***MYST3*** Q1678*	***NOTCH2*** P227H
NOTCH3 L1519P	***SOX10*** E359D	***SPTA1*** D744A	***TGFBR2*** E125fs*38		

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

DNA Gene List: For the Detection of Select Rearrangements

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

Additional Assays: For the Detection of Select Cancer Biomarkers

Microsatellite status
Tumor Mutation Burden

For more comprehensive information please log on to the Interactive Cancer Explorer™
To set up your Interactive Cancer Explorer account, contact your sales representative or call 1-888-988-3639.

APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

The median exon coverage of this sample is 533x.

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

*95% Confidence Interval

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

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

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

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

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

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

Tumor 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 and may be reported as “TMB-High”, “TMB-Intermediate”, “TMB-Low”, or “Cannot Be Determined”. TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to fewer than or equal to 5 Muts/Mb. Tumor Mutation Burden is reported as “Cannot Be Determined” 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.

For more comprehensive information please log on to the Interactive Cancer Explorer™
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APPENDIX

ABOUT FOUNDATIONONE™

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

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal): An alteration denoted as "amplification – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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

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

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

Level of Evidence Not Provided: Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

No Guarantee of Clinical Benefit: This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

No Guarantee of Reimbursement: Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne.

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

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

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

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

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