ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Lung adenocarcinoma
NAME A
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID H21 05757 1I
SPECIMEN TYPE Block
DATE OF COLLECTION 16 July 2021
SPECIMEN RECEIVED 20 August 2021

Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - 34 Muts/Mb

Genomic Findings

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

ERBB2 G776>VC
ATM S2408L
CTNNB1 S45del
ASXL1 G645fs*58, R549fs*2
CUL3 L210fs*20
FLCN R477*
FUBP1 S11fs*43
PTPRO Q484fs*14
SMARCA4 R1243W

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, KRAS, MET, RET, ROS1***

18 Therapies with Clinical Benefit
1 Therapies with Lack of Response
39 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Atezolizumab	1	Avelumab
	Cemiplimab	1	
	Durvalumab	1	
	Nivolumab	1	
	Pembrolizumab	1	
10 Trials *see p. 24*	Dostarlimab		
Tumor Mutational Burden - 34 Muts/Mb	Atezolizumab	1	Avelumab
	Cemiplimab	1	
	Durvalumab	1	
	Nivolumab	1	
	Nivolumab + Ipilimumab	1	
	Pembrolizumab	1	
10 Trials *see p. 26*	Dostarlimab		

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ERBB2 **-** G776>VC	Afatinib	Ado-trastuzumab emtansine 2A Fam-trastuzumab deruxtecan 2A Neratinib Trastuzumab Trastuzumab + Pertuzumab ⚠ Lapatinib[1]
10 Trials *see p. 32*		
ATM **-** S2408L	none	Niraparib Olaparib Rucaparib Talazoparib
10 Trials *see p. 28*		
CTNNB1 **-** S45del	none	none
10 Trials *see p. 30*		

⚠ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

FLCN **-** R477* p. 8

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

ASXL1 **-** G645fs*58, R549fs*2 p. 7

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER

Microsatellite status

RESULT
MSI-High

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] .

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[12-17], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[18-21]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[12]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[22]. 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[22-24]. This sample 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[25-27]. 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[22,24,26-27].

POTENTIAL GERMLINE IMPLICATIONS

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[22], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[28]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[28-30] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[31-33]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
34 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[34-36], anti-PD-1 therapies[34-37], and combination nivolumab and ipilimumab[38-43]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[11,34-35,38-40,44-50]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[51], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[52], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[53]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[54]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[55-56], several other large studies did find a strong association with increased TMB[57-60]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[61]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[55]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[62]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[62-63].

FINDING SUMMARY

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[64-65] and cigarette smoke in lung cancer[11,66], treatment with temozolomide-based chemotherapy in glioma[67-68], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[69-73], and microsatellite instability (MSI)[69,72-73]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[11,34-35,38-40,44-50,54,74-83].

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GENE
ERBB2

ALTERATION
G776>VC

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
2326_2327insTGT

VARIANT ALLELE FREQUENCY (% VAF)
31.9%

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[84-89], pertuzumab in combination with trastuzumab[86,90-92], and zanidatamab (ZW25)[93], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[94] and fam-trastuzumab deruxtecan[95], HER2 kinase inhibitors such as tucatinib[96-99], and dual EGFR/HER2 kinase inhibitors such as lapatinib[100-108], afatinib[89,109-118], neratinib[119-122], dacomitinib[123], and pyrotinib[124-125] . Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[126-127]. A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17.4% (4/23) for ERBB2-altered solid tumors, with PRs in 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[128]. Clinical data in solid tumors other than NSCLC and extra-mammary Pagets disease of the skin are limited; a Phase 2 study of afatinib for patients with solid tumors and ERBB2 activating mutations reported an ORR of 2.7% and a 6-month progression-free survival rate of 11%, missing its primary endpoint[129]. Second-generation TKIs dacomitinib and neratinib have elicited modest response rates in patients with ERBB2 exon 20 insertions, with reported ORRs of 3.8% to 12%, DCRs of 20% to 42.3% across two studies, and median PFS of 3.0 to 5.5 months for patients with NSCLC[121,123]. Phase 2 studies of poziotinib, a selective inhibitor targeting EGFR and ERBB2 exon 20 mutations reported ORRs of 35% to 42%, DCRs of 82% to 83%, and median PFS of 5.5 to 5.6 months in NSCLC harboring ERBB2 exon 20 insertions[130]. The irreversible ERBB inhibitor pyrotinib achieved ORRs of 32% to 53%, DCRs of 40% to 73%, and median PFS of 6.4 to 6.8 months in Phase 2 studies in previously treated, ERBB2-mutated NSCLC, with responses observed across a variety of exon 20 insertions and point mutations[131]. A Phase 2 study of EGFR/ERBB2 inhibitor tarloxotinib reported a 22.2% (2/9) ORR and a 66.7% (6/9) DCR in NSCLC with ERBB2 exon 20 insertions[132]. Antibodies targeting ERBB2 have also been tested against exon 20 insertions. Phase 2 studies have reported activity for T-DM1 in previously treated, ERBB2-mutated NSCLC, including for patients with ERBB2 exon 20 insertions[133-134]. Several case studies also report benefit from trastuzumab for patients with lung or breast cancer harboring ERBB2 exon 20 insertions[89,135-137]. Second-generation TKI afatinib has elicited modest response rates in patients with ERBB2 exon 20 insertions, with reported ORRs of 7.7% to 33.3% and DCRs of 53.8% to 69.6% across several studies, and median PFS of 3.2 to 4.5 months for patients with NSCLC[114-118]. Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib[89,115-116,121,123,130,138-142]. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab.

FREQUENCY & PROGNOSIS

ERBB2 mutations have been reported in 2.2–4.2% of lung adenocarcinomas and lung squamous cell carcinomas across several genomic studies[47,59,143-146]. Exon 20 insertions are the most frequently observed ERBB2 alteration in lung adenocarcinomas, representing 61% (72/118) to 96% (24/25) of ERBB2 mutations detected[117,147]. One large study of 20,656 patients with non-small cell lung cancer reported 24% of ERBB2 mutations were exon 20 insertions[148]. Of ERBB2 exon 20 insertions in NSCLC, A775_G776insYVMA is the most common (42–85%), followed by P780_Y781insGSP (9–11%) and G776>VC (8–11%)[116-117,130,147]. Exon 20 insertion mutations are more prevalent in adenocarcinoma histology[116] and are generally mutually exclusive with other common driver alterations in NSCLC[147]. HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[149-150]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[151-155]. In a retrospective study of patients with ERBB2-mutated NSCLC who were treated with afatinib, A775_G776insYVMA predicted inferior PFS when compared with other exon 20 insertions (HR = 0.009) or missense mutations (HR = 0.184), whereas P780_Y781insGSP and G776>VC were associated with improved PFS compared with missense mutations (HR = 0.050)[117].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. ERBB2 exon 20 insertion mutations, such as observed here, are predicted to be activating[130,140,156-158]. The mutation seen here is similar to G776>VC (also known as G776_V777>VCV, G776delinsVC, or G776_V777delinsVCV)[130].

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GENE
ATM

ALTERATION
S2408L

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
7223C>T

VARIANT ALLELE FREQUENCY (% VAF)
25.2%

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[159]. Clinical data in prostate cancer[160-162], gastric cancer[163], colorectal cancer[164], breast cancer[164], papillary renal cell carcinoma[165], and cholangiocarcinoma[166] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[167-174]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[175] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[176] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[177-179] and hematologic malignancies[177,180] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[181]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 8-11% of lung adenocarcinomas[58-59,144] and 5% of lung squamous cell carcinomas (SCCs)[146]. Expression of ATM protein has been reported to be significantly higher in non-small cell lung carcinoma samples than in normal tissues[182]. In one study, higher ATM protein levels in lung SCC, but not in lung adenocarcinoma, significantly correlated with shorter disease-free and overall survival of patients treated with cisplatin[183].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[184]. Loss of functional ATM promotes tumorigenesis[185]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[186]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[187]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[184,187]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[187]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[188-193]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[192,194-195]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
CTNNB1

ALTERATION
S45del

TRANSCRIPT ID
NM_001904

CODING SEQUENCE EFFECT
133_135delTCT

VARIANT ALLELE FREQUENCY (% VAF)
56.0%

POTENTIAL TREATMENT STRATEGIES
Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[196-198]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[199-200] or endometrial carcinoma[201]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[202-204]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate in 2 out of 4 patients and SD rate of in 1 out of 4 patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[205]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[206-209]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[210-211], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[197,212-214].

FREQUENCY & PROGNOSIS
CTNNB1 mutations have been reported in 4% of lung adenocarcinomas[144] and in 2% of lung squamous cell carcinomas[146]. One study reported aberrant beta-catenin immunostaining in 47% of lung adenocarcinomas[215]. Aberrant beta-catenin expression has been associated with poor prognosis in patients with lung adenocarcinoma and other non-small cell lung carcinomas[216-218]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[219].

FINDING SUMMARY
CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[220]. CTNNB1 exon 3 mutations, such as observed here, lead to increased beta-catenin protein stability and activation of the WNT pathway, and are considered to be activating[221-239].

GENE
ASXL1

ALTERATION
G645fs*58, R549fs*2

TRANSCRIPT ID
NM_015338, NM_015338

CODING SEQUENCE EFFECT
1934delG, 1644_1645insT

VARIANT ALLELE FREQUENCY (% VAF)
20.1%, 50.6%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in ASXL1.

FREQUENCY & PROGNOSIS
ASXL1 alterations occur infrequently across various solid tumor types[240] and are not known to act as drivers in any specific solid cancer type[241]. Published data investigating the prognostic implications of ASXL1 alterations in solid tumors are limited (PubMed, May 2021). In the context of clonal hematopoiesis, ASXL1 mutations are significantly enriched in current or former smokers[242].

FINDING SUMMARY
ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors[243-245]. Alterations such as seen here may disrupt ASXL1 function or expression[246-248].

POTENTIAL CLONAL HEMATOPOIESIS

IMPLICATIONS
Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[188-193]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[188-189]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[249]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[192,194-195]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
CUL3

ALTERATION
L210fs*20

TRANSCRIPT ID
NM_003590

CODING SEQUENCE EFFECT
629_630insT

VARIANT ALLELE FREQUENCY (% VAF)
33.5%

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to directly address genomic alterations in CUL3.

FREQUENCY & PROGNOSIS
Mutations affecting CUL3-KEAP1 complex formation and regulation of the stress-regulated transcription factor NRF2 have been found in 4/5 cases of sporadic papillary renal cell carcinoma[250]. Mutations affecting the CUL3-KEAP1 complex have also been reported in lung cancer, and linked to increased NF-kB signaling through upregulation of IkkB protein expression[251]. Decreased CUL3 expression has been linked to an aggressive phenotype in bladder cancer models[252] and to formation of hepatocellular carcinomas through regulation of cyclin E expression[253].

FINDING SUMMARY
CUL3 encodes the RING ubiquitin ligase cullin 3, which has been shown to form complexes regulating diverse cellular processes, including development and stress responses.

GENE
FLCN

ALTERATION
R477*

TRANSCRIPT ID
NM_144997

CODING SEQUENCE EFFECT
1429C>T

VARIANT ALLELE FREQUENCY (% VAF)
36.7%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies approved or in clinical trials that directly address genomic alterations in FLCN. Folliculin deficiency in renal cancer cells has been shown to be associated with sensitivity to radiation[254] and taxane chemotherapy[255].

FREQUENCY & PROGNOSIS
FLCN mutations have been detected in several tumor types, including tumors of the large intestine (3.1%), endometrium (3.1%), stomach (2.5%), and skin (2.5%)(COSMIC, 2021)[256]. Additionally, several studies have reported sporadic FLCN mutations in 0.0% (0/8)-23% (7/30) of colorectal and gastric cancers with microsatellite instability[257-260]. Published data investigating the prognostic implications of FLCN alterations in cancer are limited (PubMed, Feb 2021).

FINDING SUMMARY
FLCN encodes the tumor suppressor protein folliculin, which forms a complex with either the FNIP1 or FNIP2 protein and interacts with AMP-activated protein kinase (AMPK), an energy-sensing molecule that monitors the AMP/ATP ratio in the cell and regulates the activity of the mTOR pathway[261-263]. FLCN inactivating mutations, including protein truncating mutations, missense mutations, deletions, and duplications, have been described in families with Birt-Hogg-Dubé (BHD) syndrome[264-265]. FLCN has also been described as a mutational target in cancers with microsatellite instability[257-258].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the FLCN variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with multiple fibrofolliculomas (ClinVar, Mar 2021)[266]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline loss-of-function alterations in FLCN are associated with Birt-Hogg-Dubé (BHD) syndrome, a condition characterized by cutaneous lesions such as fibrofolliculomas, renal and lung hamartomas, renal cancers, pulmonary cysts, and pneumothorax[267-268]. Indels in exon 11 are common[269], but large deletions have also been identified[270-271]. Skin lesions typically appear early in life, increasing in size and number with age, but may not be present in all families[272]. Individuals with BHD syndrome are at a seven-fold increased risk for renal tumors, with a lifetime risk of 16%; median age of renal tumor diagnosis is 48 years[272-273]. Most BHD-associated renal tumors display mixed chromophobe/oncocytic histology[272]. In the appropriate clinical context, germline testing of FLCN is recommended.

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GENE
FUBP1

ALTERATION
S11fs*43

TRANSCRIPT ID
NM_003902

CODING SEQUENCE EFFECT
30delC

VARIANT ALLELE FREQUENCY (% VAF)
39.5%

POTENTIAL TREATMENT STRATEGIES
Therapies targeting FUBP1 mutation directly or downstream effectors have not been tested preclinically or clinically in tumors that harbor FUBP1 mutations.

FREQUENCY & PROGNOSIS
FUBP1 alteration has been reported in 1.5% of samples analyzed in COSMIC, with the highest incidences reported in tumors of the meninges (6%), endometrium (3%), central nervous system (3%), large intestine (3%), stomach (3%), liver (3%), and skin (2%) (COSMIC, 2021)[256]. One study reported higher expression of FUBP1 in colorectal carcinoma tissues compared to adenoma and normal colon epithelial tissues[274]. A genetic signature defined by concomitant alterations in IDH1, CIC, and FUBP1 is associated with longer survival in patients with glioma[275]. FUBP1 has been shown to activate the expression of MYC[276-279], activate p27KIP1[280], and regulate the splicing of MDM2[281].

FINDING SUMMARY
FUBP1 encodes far upstream element binding protein 1 (also called FBP-1), a DNA-binding protein reported to have roles in transcriptional activation and splicing regulation of target genes. It is believed to act as an oncogene in some tumor types, such as hepatocellular carcinoma and non-small-cell lung cancer[282-283], and as a tumor suppressor in others, particularly oligodendroglioma, for which mutations and/or loss of FUBP1 often co-occur with alterations in CIC or IDH1[275,284-287].

GENE
PTPRO

ALTERATION
Q484fs*14

TRANSCRIPT ID
NM_030667

CODING SEQUENCE EFFECT
1448_1449insA

VARIANT ALLELE FREQUENCY (% VAF)
33.6%

POTENTIAL TREATMENT STRATEGIES
No targeted therapies are available to address genomic alterations in PTPRO. In a preclinical study of breast cancer, PTPRO expression was suppressed by estrogen but increased by tamoxifen; upregulation of PTPRO sensitized cells to this selective estrogen modulator[288]. Low PTPRO expression has been implicated in resistance to cetuximab in patients with KRAS wild-type colorectal carcinoma[289].

FREQUENCY & PROGNOSIS
In the TCGA datasets, PTPRO mutation has been reported at highest frequency in lung squamous cell carcinoma (SCC, 6.2%)[146], uterine corpus endometrial carcinoma (UCEC, 5.4%)[69], and lung adenocarcinoma (3%)[144], whereas homozygous deletion was most frequently identified in cases of lung (3%)[144] or prostate (1.8%)[290] adenocarcinoma. Hypermethylation of the PTPRO promoter is also observed in breast[288,291-292], hepatocellular[293-294], colorectal[295], esophageal squamous cell[296], and lung squamous cell carcinoma (SCC)[297] as well as in some leukemias[298-299]. Promoter methylation significantly correlates with reduced PTPRO transcript levels[291-293,300-301] and is associated with poor prognosis in patients with lung SCC[297] and breast cancer[291,300,302]; in the context of the latter, epigenetic silencing of PTPRO is an independent predictor of shorter overall survival (OS) for patients with HER2-positive disease[291,302]. Low PTPRO expression in breast cancer is also significantly associated with shorter OS and poor prognosis[300] and in lung SCC is an independent predictor of the latter[297].

FINDING SUMMARY
PTPRO, also known as GLEPP1 , encodes a protein tyrosine phosphatase that regulates podocyte function[303-304]. In the context of cancer, PTPRO is a tumor suppressor that attenuates signaling and tumorigenesis by multiple oncogenes, through dephosphorylation and/or endocytic downregulation of these substrates[292,300-301,305].

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GENE
SMARCA4

ALTERATION
R1243W

TRANSCRIPT ID
NM_003072

CODING SEQUENCE EFFECT
3727C>T

VARIANT ALLELE FREQUENCY (% VAF)
33.5%

POTENTIAL TREATMENT STRATEGIES

Clinical[306] and preclinical[307-313] data suggest that patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with EZH2 inhibitors, including tazemetostat. In addition, preclinical data have demonstrated that SMARCA4-deficient non-small cell lung cancer (NSCLC) and SCCOHT patient-derived xenografts and cell lines are highly sensitive to CDK4/6 inhibition through a synthetic lethal mechanism of reduced cyclin D1 expression[314-315]. Notably, similar drug sensitivity was detected in SMARCA4-deficient lung and ovarian tumors, thereby suggesting that SMARCA4-deficient tumors are likely to be sensitive to CDK4/6 inhibition regardless of tissue of origin[314-315]. Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[316]. 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[317].

FREQUENCY & PROGNOSIS

In the TCGA datasets, SMARCA4 mutations have been reported in 6% of lung adenocarcinomas[144] and in 5% of lung squamous cell carcinomas[146]. Loss of BRG1 protein expression has been observed in 10-15% of non-small cell lung cancer (NSCLC) cases in the scientific literature[318-320]. Loss of expression of BRG1 and BRM, another catalytic subunit in SWI/SNF chromatin remodeling complexes, has been correlated with poor prognosis in patients with NSCLC[318-319,321-322].

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[323]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[324]. Alterations such as seen here may disrupt SMARCA4 function or expression[325-329].

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Afatinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[114-118,130,140-142] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[114-118] . Retrospective data suggest that ERBB2 G776>VC or P780_Y781insGSP may predict improved PFS with afatinib in patients with NSCLC as compared with ERBB2 missense mutations (HR = 0.050)[117].

SUPPORTING DATA

The Phase 2 NICHE trial for platinum-refractory NSCLC harboring ERBB2 exon 20 insertions reported a low ORR but a high DCR, with 1 PR and 7 SDs out of 13 patients; the median PFS and OS were 3.7 and 13 months, respectively[114]. A retrospective study of afatinib in patients with ERBB2-mutated NSCLC, most of whom were previously treated, reported an ORR of 16% and a DCR of 69%; the median PFS was 1.2 months for patients with A775_G776insYVMA, 7.6 months for patients with G776>VC or P780_Y781insGSP, and 3.6 months for patients with ERBB2 missense mutations[117]. Other retrospective studies of afatinib in ERBB2-mutated lung cancer have reported similar ORRs of 13–16% and DCRs of 68–70%[115-116] . Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[330-336] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[89,111-115,117-118,138,140,337-338] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[335]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[339].

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Atezolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data showing efficacy of atezolizumab alone or in combination with antiangiogenic therapy for patients with MSI-H colorectal cancer[3] or endometrial cancer[4], MSI-H status may predict sensitivity to atezolizumab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[341-343] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[342]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[341]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[343]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[344]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[345], confirming previous Phase 2 trial data[346-347] . Clinical benefit was observed for patients regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[345]. Retrospective analyses of the OAK trial additionally identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[348], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[349]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected early-stage NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[350]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 TPS ≥50%[351].

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Cemiplimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[7,9-10,352-355] , MSI-H status may predict sensitivity to cemiplimab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[356]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[357].

Dostarlimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] . On the basis of prospective clinical data showing efficacy of dostarlimab against various microsatellite instability-high (MSI-H) solid tumors[358-361] , MSI-H status may predict sensitivity to dostarlimab.

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[359]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[358,360,362] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[360,363] .

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Durvalumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable NSCLC who did not have progression on chemoradiotherapy (CT), durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; PFS was 17.8 versus 5.6 months (HR=.46) for patients with PD-L1 expression ≥1%, and 10.7 versus 5.6 months (HR=.73) for patients with PD-L1 expression <1%. OS benefit was observed for patients with PD-L1 expression ≥1% (not reached [NR] vs. 29.6 months, HR=0.59), but not for those with PD-L1 expression <1% (33.1 vs. 45.6 months, HR=1.14)[364]. In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[365]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[365]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 and 0.85, respectively); however, patients with bTMB ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[366]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[367-368] and OS[367] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 30.9% (21/68), compared with ORRs of 16.4% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity, respectively[368]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR- or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25.0% (10/40) of patients[369].

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Nivolumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[7,9] , MSI-H status may predict sensitivity to nivolumab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

In patients with advanced non-small cell lung cancer (NSCLC) and at least 5% PD-L1 expression, although first-line nivolumab did not improve median PFS (4.2 vs. 5.9 months, HR=1.15) or OS (14.4 vs. 13.2 months, HR=1.02) in the overall population as compared with investigator's choice of platinum-based doublet chemotherapy, patients with elevated TMB (TMB ≥13 muts/Mb) experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)[46]. A study of neoadjuvant nivolumab for patients with resectable NSCLC reported that major pathologic responses occurred in 45.0% (9/20) of patients and significantly correlated with TMB[48]. For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[370]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[371-372] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[373]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[374], despite Phase 1 results in the same setting suggesting improved ORR and OS[375]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[376].

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Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and pleural mesothelioma. Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[38-39,377] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

The Phase 3 CheckMate 227 study of nivolumab plus ipilimumab for patients with advanced non-small cell lung cancer (NSCLC) reported improved median OS relative to chemotherapy (17.1 vs. 13.9 months, HR=0.73) regardless of PD-L1 positivity, TMB status, or brain metastases[52,378] , despite earlier analysis of this trial that suggested improved PFS only for patients with TMB ≥10 Muts/Mb (as measured by this assay)[39]. Similar results were observed in the Phase 3 CheckMate 9LA study, which observed significantly improved 2-year OS (38% vs. 26%), median PFS (6.7 months vs. 5.3 months), and ORR (38% vs. 25%) for patients treated with nivolumab plus ipilimumab in combination with chemotherapy when compared with patients treated with chemotherapy alone[379].

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Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden-high (TMB-High; ≥10 Muts/Mb), microsatellite instability-high (MSI-High), or mismatch repair deficient (dMMR) solid tumors, or PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma, cervical cancer, gastric cancer, esophageal cancer, or gastroesophageal junction (GEJ) carcinoma. It is also approved in various treatment settings for patients with melanoma, NSCLC, small cell lung cancer, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, or cutaneous squamous cell carcinoma (CSCC). Combination treatments with pembrolizumab are approved for patients with NSCLC, renal cell carcinoma, endometrial carcinoma that is not MSI-High or dMMR, or triple-negative breast cancer (TNBC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against MSI-H or mismatch repair-deficient (dMMR) solid tumors[10,352-355,380] , MSI-H status may predict sensitivity to pembrolizumab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[381] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[382], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[382]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[383]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[384]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[385] or squamous (KEYNOTE-407)[386-387] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[51]; exploratory analysis of KEYNOTE-189 demonstrated superiority of the pembrolizumab combination therapy regardless of blood TMB (bTMB) status[388]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[389]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[390]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single-agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[391-393] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[394], the anti-CTLA-4 antibody ipilimumab[395], the anti-TIGIT antibody vibostolimab[396], the HDAC inhibitor vorinostat[397], and the multikinase inhibitor lenvatinib[398].

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Ado-trastuzumab emtansine

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1. Patients with NSCLC and various ERBB2 exon 20 insertion mutations have benefited from T-DM1[133-134,399] .

SUPPORTING DATA

In a Phase 2 basket trial of T-DM1, patients with ERBB2-mutated and/or -amplified NSCLC achieved an ORR of 51.0% (25/49) and a median PFS of 5 months, with similar response rates across subgroups[400]. Another Phase 2 trial in chemotherapy-refractory HER2-positive NSCLC reported an ORR of 6.7% and a median PFS of 2.0 months; patients with HER2 expression experienced an ORR and a DCR of 0% (0/8) and 37.5% (3/8), and no patients experienced tumor shrinkage, whereas patients with ERBB2 exon 20 insertion mutations experienced an ORR and a DCR of 14.3% (1/7) and 71.4% (5/7), respectively[134]. A patient with NSCLC, disease progression on 2 prior lines of chemotherapy, and ERBB2 amplification and A775_G776insYVMA mutation experienced a rapid and durable response to T-DM1[138,399] .

Avelumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
34 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab. On the basis of clinical data across solid tumors[35-37,78,340] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[35-36] .

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[401], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[402]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[403]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[404]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[405]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[406]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[407].

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Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[408], ERBB2 mutation may predict sensitivity to fam-trastuzumab deruxtecan. A Phase 1 study of fam-trastuzumab deruxtecan reported a 75% (6/8) ORR for patients with non-small cell lung cancer and ERBB2 exon 20 mutations[408].

SUPPORTING DATA

In the Phase 2 DESTINY-Lung01 study of single-agent fam-trastuzumab deruxtecan for patients with ERBB2-altered non-small cell lung cancer (NSCLC), the ERBB2-mutated cohort reported a 62% (26/42; 1 CR, 25 PR) ORR and a 91% (38/42) DCR[409], and the ERBB2-overexpressing cohort reported a 25% (12/49) ORR and a 69% (34/49) DCR[410]. In a previous Phase 1 study evaluating fam-trastuzumab deruxtecan in non-breast and non-gastric solid tumors, patients with ERBB2-expressing or -mutated NSCLC experienced a 56% (10/18) ORR and an 83% (15/18) DCR, with a median PFS of 11.3 months[411]. In this study, the ORR was 73% (8/11) for patients with ERBB2-mutated NSCLC, with 6 responses reported for patients with ERBB2 exon 20 insertions[411]. A patient with lung cancer harboring both ERBB2 amplification and the S310F mutation who had progressed on ado-trastuzumab emtansine after 4 months was treated with fam-trastuzumab deruxtecan and exhibited a PR that lasted for 1 year[400].

Neratinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

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 (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[119-122,412-414] and preclinical[158,415-418] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib. A Phase 2 trial of neratinib in patients with solid tumors reported 1 CR, 1 PR, and 14 SD out of 25 evaluable patients with ERBB2 exon 20 insertion mutations, with both objective responses in patients with breast cancer[121]. Preclinical data support reduced sensitivity of ERBB2 exon 20 insertions to neratinib[130,141] .

SUPPORTING DATA

In the Phase 2 SUMMIT trial of neratinib in patients with ERBB2 or ERBB3 mutations, the ORR was 3.8% (1/26) and the median PFS was 5.5 months for patients with NSCLC, most of whom harbored ERBB2 exon 20 insertions; PR was observed in one patient with L755S mutation[121]. A Phase 2 study in ERBB2-mutated NSCLC reported objective response and clinical benefit in 19% (8/43) and 51% (22/43) of patients treated with neratinib plus the mTOR inhibitor temsirolimus, compared with 0% (0/17) and 35% (6/17) for patients treated with single-agent neratinib; exon 20 insertions were the most common ERBB2 mutation[419-420] .

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Niraparib

Assay findings association

ATM
S2408L

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[160-162,421] , colorectal cancer[164], breast cancer[164], gastric cancer[163], cholangiocarcinoma[166], and papillary renal cell carcinoma[165]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/2 patients with non-small cell lung cancer achieved stable disease; 1/2 patients harbored a BRCA2 mutation[422]. Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[423]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[422]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[424].

Olaparib

Assay findings association

ATM
S2408L

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[160-162,421] , colorectal cancer[164], breast cancer[164], gastric cancer[163], cholangiocarcinoma[166], and papillary renal cell carcinoma[165]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 2 study, the addition of olaparib to gefitinib did not significantly increase either median PFS (10.9 vs. 12.8 months; HR 0.75, p=0.12) or median OS (23.1 vs. 23.3 months; HR 1.22, p=0.346) in patients with EGFR-mutant NSCLC, unselected for other mutations; the ORR for patients treated with the combination (71%, 60/84) was similar to that of those treated with single-agent gefitinib (68%, 61/90)[425].

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Rucaparib

Assay findings association

ATM
S2408L

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[160-162,421] , colorectal cancer[164], breast cancer[164], gastric cancer[163], cholangiocarcinoma[166], and papillary renal cell carcinoma[165]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of rucaparib in advanced NSCLC closed due to futility; the reported ORR was 7% (n=59) for patients with BRCA-mutated or high genomic loss of heterozygosity[426]. Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[427]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[428]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[429]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[430]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[431]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[432]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[433]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[434].

Talazoparib

Assay findings association

ATM
S2408L

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[160-162,421] , colorectal cancer[164], breast cancer[164], gastric cancer[163], cholangiocarcinoma[166], and papillary renal cell carcinoma[165]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of talazoparib in patients with squamous cell lung cancer harboring homologous recombination repair deficiency reported modest activity with an ORR of 11% (5/47), a DCR of 53% (25/47), a median PFS of 2.5 months and a median OS of 5.7 months[435].

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Trastuzumab

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

Trastuzumab-involving regimens elicited significant responses in patients with certain ERBB2 mutations[88-89,104,135,138,436] . Patients with NSCLC and ERBB2 exon 20 insertions, including A775_G776insYVMA and G776>VC, have benefited from treatment with trastuzumab[88-89,135-136,138] , with reported DCRs of 75–96% for trastuzumab in combination with chemotherapy[89,138] .

SUPPORTING DATA

In a Phase 2a basket trial (MyPathway), trastuzumab plus pertuzumab treatment in non-small cell lung cancer (NSCLC) elicited PRs in 2/16 patients with ERBB2 amplification or overexpression and in 3/14 patients with HER2 mutation[437]. A Phase 2 trial of docetaxel with trastuzumab for the treatment of NSCLC reported PRs for 8% of patients, although the response did not correlate with HER2 status as assessed by immunohistochemistry[438]. Another Phase 2 study of 169 patients with NSCLC reported an ORR of 23% (7/30) with combination therapy of docetaxel and trastuzumab and 32% (11/34) with paclitaxel and trastuzumab; HER2 expression did not impact the results of this study[439]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a PR on trastuzumab and paclitaxel[87]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[89].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[91,437,440-444] .

SUPPORTING DATA

In a Phase 2a basket trial (MyPathway), trastuzumab plus pertuzumab treatment in non-small cell lung cancer (NSCLC) elicited partial responses (PRs) in 2/16 patients with ERBB2 amplification or overexpression and in 3/14 patients with HER2 mutation[437].

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Lapatinib

⚠ Patient may be resistant to Lapatinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[100-108] . On the basis of clinical and preclinical evidence, ERBB2 exon 20 insertions confer resistance to lapatinib[89,130,138-141] . However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab.

SUPPORTING DATA

Prospective[139] and retrospective studies[89,138] reported PD for multiple patients with NSCLC and ERBB2 exon 20 insertions treated with lapatinib in either the first or later line setting. Clinical data on the efficacy of lapatinib have primarily been in the context of breast cancer. A Phase 1 study lapatinib monotherapy included 9 unselected patients with lung cancer and reported 1 case of prolonged SD[445]. Additionally, patients with ERBB2-mutated lung cancer have experienced limited partial responses to lapatinib plus chemotherapy in case reports[100,103,446] . In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted[447].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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Electronically signed by Tyler Janovitz, MD, PhD | 26 August 2021
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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

BIOMARKER

Microsatellite status

RATIONALE
High microsatellite instability (MSI) may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) and anti-PD-L1 immune checkpoint inhibitors.

RESULT
MSI-High

NCT03800134

PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), San José (Costa Rica), Temuco (Chile), Buenos Aires (Argentina), Guatemala (Guatemala)

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: San Isidro (Peru), Lima (Peru), Arequipa (Peru), Ijui (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Cdmx (Mexico), Mexico (Mexico), Querétaro (Mexico), Florida

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

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NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Florida, Hsinchu (Taiwan), Missouri, Illinois, Kharkiv (Ukraine), Kryvyi Rih (Ukraine)

NCT03425643

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage IIB or IIIA Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)

TARGETS
PD-1

LOCATIONS: San Juan (Argentina), Cordoba (Argentina), Rosario (Argentina), Ijui (Brazil), Berazategui (Argentina), Brasilia (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Florianopolis (Brazil), Sao Paulo (Brazil)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico), San Juan (Puerto Rico), Ipatinga (Brazil)

NCT04513925

PHASE 3

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
TIGIT, PD-L1

LOCATIONS: Cordoba (Argentina), Sao Jose do Rio Preto (Brazil), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Curitiba (Brazil), Porto Alegre (Brazil), Sao Paulo (Brazil), Florida, Fortaleza (Brazil)

NCT03924869

PHASE 3

Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Medically Inoperable Stage I or IIA Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)

TARGETS
PD-1

LOCATIONS: Rosario (Argentina), Buenos Aires (Argentina), Porto Alegre (Brazil), Campinas (Brazil), Sao Paulo (Brazil), Rio de Janeiro (Brazil), Florida, Alabama, Tennessee

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BIOMARKER

Tumor Mutational Burden

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

RESULT

34 Muts/Mb

NCT03800134

PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), San José (Costa Rica), Temuco (Chile), Buenos Aires (Argentina), Guatemala (Guatemala)

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: San Isidro (Peru), Lima (Peru), Arequipa (Peru), Ijui (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Cdmx (Mexico), Mexico (Mexico), Querétaro (Mexico), Florida

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Ciudad Autonoma De Buenos Aire (Argentina), Texas, Alabama, Georgia, South Carolina, North Carolina, Tennessee, Kentucky

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida

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NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Florida, Hsinchu (Taiwan), Missouri, Illinois, Kharkiv (Ukraine), Kryvyi Rih (Ukraine)

NCT03425643

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage IIB or IIIA Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)

TARGETS
PD-1

LOCATIONS: San Juan (Argentina), Cordoba (Argentina), Rosario (Argentina), Ijui (Brazil), Berazategui (Argentina), Brasilia (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Florianopolis (Brazil), Sao Paulo (Brazil)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico), San Juan (Puerto Rico), Ipatinga (Brazil)

NCT04513925

PHASE 3

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
TIGIT, PD-L1

LOCATIONS: Cordoba (Argentina), Sao Jose do Rio Preto (Brazil), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Curitiba (Brazil), Porto Alegre (Brazil), Sao Paulo (Brazil), Florida, Fortaleza (Brazil)

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GENE
ATM

ALTERATION
S2408L

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Lima (Peru), Trujillo (Peru), Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina), Berazategui (Argentina)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Lima (Peru), Bellavista (Peru), Cuzco (Peru), Arequipa (Peru), Cali (Colombia), Medellin (Colombia), Bucaramanga (Colombia), La Rioja (Argentina), Barranquilla (Colombia), Ciudad de Buenos Aires (Argentina)

NCT04475939

PHASE 3

Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants With Advanced/Metastatic Non-small Cell Lung Cancer

TARGETS
PD-1, PARP

LOCATIONS: Rosario (Argentina), Cipoletti (Argentina), Florida (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), Curitiba (Brazil), Porto Alegre (Brazil), Belo Horizonte (Brazil), Cachoeiro Do Itapemirim (Brazil), Texas, Georgia

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

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ORDERED TEST # ORD-1171465-01

CLINICAL TRIALS

NCT03329001

PHASE 1

Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Compared to Niraparib Capsule

TARGETS
PARP

LOCATIONS: Florida, Georgia, Texas, Tennessee, Oklahoma, Connecticut, Michigan, Colorado, California

NCT02498613

PHASE 2

A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors

TARGETS
PARP, VEGFRs

LOCATIONS: Florida, Texas, Tennessee, Virginia, Connecticut, Massachusetts, Toronto (Canada), California

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Florida, Texas, Georgia, Virginia, New York, Ohio, Massachusetts, Quebec (Canada)

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: Florida, Tennessee, Missouri, Pennsylvania, Connecticut, Massachusetts, California

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
PARP

LOCATIONS: Texas, North Carolina, Tennessee, New York, Rhode Island, Massachusetts, Toronto (Canada), Manchester (United Kingdom), London (United Kingdom), Newcastle Upon Tyne (United Kingdom)

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GENE
CTNNB1

ALTERATION
S45del

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Texas, Tennessee, Virginia, District of Columbia, Maryland, Missouri, Pennsylvania, New York, Massachusetts

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT04250545

PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS
mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

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NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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GENE
ERBB2

ALTERATION
G776>VC

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors. Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab. Retrospective clinical data suggest that ERBB2 G776>VC or P780_Y781insGSP is associated with improved PFS on afatinib, compared with other ERBB2 mutations or exon 20 insertions. In addition, clinical data suggests reduced sensitivity of ERBB2 G776>VC to dacomitinib. Investigational agents such as poziotinib and pyrotinib, or ERBB2-targeted antibodies such as trastuzumab and T-DM1, may be more effective.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Sao Paulo (Brazil), Florida, Alabama, Texas, Georgia, South Carolina

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Florida, Louisiana, Tennessee, Texas, New Jersey, Missouri

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, KIT, RET, VEGFRs, EGFR, ERBB2, ERBB4, MET, ROS1

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT03318939

PHASE 2

Phase 2 Study of Poziotinib in Patients With NSCLC With EGFR or HER2 Exon 20 Insertion Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Florida, Texas, Georgia, North Carolina, Virginia, District of Columbia, Maryland

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NCT02716116

PHASE 1/2

A Trial of AP32788 in Non-Small Cell Lung Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: Florida, Georgia, North Carolina, Virginia, Arizona, California

NCT01953926

PHASE 2

An Open-label, Phase 2 Study of Neratinib in Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations or EGFR Gene Amplification

TARGETS
EGFR, ERBB2, ERBB4, ER

LOCATIONS: Louisiana, Texas, Georgia, Alabama, Tennessee, Delaware, Missouri, Pennsylvania

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: South Carolina, North Carolina, Texas, Tennessee, Virginia, Missouri, Pennsylvania, New York, Ohio

NCT03066206

PHASE 2

Poziotinib in EGFR Exon 20 Mutant Advanced Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Texas

NCT03805841

PHASE 2

Phase 2 Study of Tarloxotinib in Patients With NSCLC Harboring EGFR Exon 20 Insertion or HER2-activating Mutations

TARGETS
ERBB2, EGFR

LOCATIONS: Georgia, District of Columbia, Pennsylvania, Michigan, Illinois, Toronto (Canada), Colorado, California

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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.

ARID1A A228T	***AXIN1*** G309S	***BRD4*** P766Q	***CARD11*** R35H
CD274 (PD-L1) A85V	***CEBPA*** H212R	***CHEK2*** L174F	***DOT1L*** G859R
ERCC4 N244D	***FANCA*** A1216T	***FGF3*** R63H	***FLT3*** E672K
GNAS T415A	***JUN*** P240fs*69	***MLH1*** A589P	***MUTYH*** C54Y
MYCL1 R247H	***NSD3 (WHSC1L1)*** K598del	***PALB2*** P267L	***PARP3*** Y527C
RB1 M705del	***RICTOR*** I880V and S1406F	***SDHA*** A278T	***SMARCA4*** R1374C
TGFBR2 K128fs*35	***TNFAIP3*** T531A	***TSC1*** K587R	

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Electronically signed by Tyler Janovitz, MD, PhD | 26 August 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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Electronically signed by Tyler Janovitz, MD, PhD | 26 August 2021
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit.

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Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides

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entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 4.2.0

The median exon coverage for this sample is 973x

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