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 Breast carcinoma (NOS)

DATE OF BIRTH 06 February 1954
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Hospital Regional Lambayeque
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 319645
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Breast
SPECIMEN ID H21-714 (Q20-7027/24)
SPECIMEN TYPE Block
DATE OF COLLECTION 10 October 2020
SPECIMEN RECEIVED 23 January 2021

Biomarker Findings

Tumor Mutational Burden - 10 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

PALB2 S254fs*3, splice site 3113+1G>A
GNA13 K42N - subclonal†

† See About the Test in appendix for details.

11 Therapies with Clinical Benefit
0 Therapies with Lack of Response
19 Clinical Trials

BIOMARKER FINDINGS

Tumor Mutational Burden - 10 Muts/Mb

10 Trials *see p. 11*

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Atezolizumab 2A	Avelumab
Pembrolizumab	Cemiplimab
	Durvalumab
	Nivolumab
	Nivolumab + Ipilimumab

Microsatellite status - MS-Stable

No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS

PALB2 - S254fs*3, splice site 3113+1G>A

10 Trials *see p. 13*

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Olaparib	Niraparib
Talazoparib	Rucaparib

☐ *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 data and were detected at an allele frequency of >10%. See appendix for details.

PALB2 - S254fs*3 ..... p. 4

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.

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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

Tumor Mutational Burden

RESULT
10 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[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-9]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[1-4,10]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[1]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[11] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[2]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[4,10]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[12]. A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors[13]. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 Muts/Mb for luminal A tumors, 1.38 Muts/Mb for luminal B tumors, 2.05 Muts/Mb for HER2-enriched tumors, and 1.68 Muts/Mb for basal-like tumors[14]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors[13,15-16]. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma[13,15-16]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[13]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[16]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[17].

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[18-19] and cigarette smoke in lung cancer[20-21], treatment with temozolomide-based chemotherapy in glioma[22-23], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[24-28], and microsatellite instability (MSI)[24,27-28]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[2-4,10].

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[29-31], including approved therapies nivolumab and pembrolizumab[32]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[33].

FREQUENCY & PROGNOSIS

MSI is extremely rare in breast cancer, reported in 0-1% of cases across studies[34-39]. The incidence of MSI is increased in triple-negative breast cancer[37-39] and in tumors with homologous recombination defects, such as mutations in BRCA1/2[37,39]. Notably, in Lynch syndrome–related breast cancer, MSI has been reported in 51-85% of cases[40-45]. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence[46].

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[47]. 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[47-49]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[50-52]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[47,49,51-52].

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GENE
PALB2

ALTERATION
S254fs*3, splice site 3113+1G>A

TRANSCRIPT ID
NM_024675, NM_024675

CODING SEQUENCE EFFECT
758_759insT, 3113+1G>A

VARIANT ALLELE FREQUENCY (% VAF)
47.6%, 25.0%

POTENTIAL TREATMENT STRATEGIES
Clinical evidence in prostate[53-55], ovarian[56], breast[57], and pancreatic cancer[58] indicates that PALB2 loss or inactivation may confer sensitivity to PARP inhibitors. Inactivation of the Fanconi anemia/BRCA pathway, including PALB2 mutations, also sensitizes cells to mitomycin C and cisplatin[59-62].

FREQUENCY & PROGNOSIS
In the TCGA datasets, PALB2 mutation has been observed in fewer than 1% of invasive breast carcinoma cases, whereas PALB2 loss has not been reported[14,63]. PALB2 truncations leading to the partial or complete loss of the WD40 domain (<1186) was reported at a frequency of 0.6-1.1% in four large studies[64-67], as well as in 1 out of 8 male patients with breast cancer[68]. Published data investigating the prognostic implications of PALB2 alteration in breast cancer are limited (PubMed, Sep 2020).

FINDING SUMMARY
PALB2, also known as FANCN (Fanconi Anemia complementation group N), encodes a BRCA2-binding protein that acts to stabilize the association of BRCA2 with chromatin and the nuclear matrix[69]. The PALB2 protein additionally acts to functionally connect BRCA1 and BRCA2 with one another in response to DNA damage; cells with defective PALB2 are deficient in the homologous recombination repair response to double-strand DNA breaks[69-72]. Alterations such as seen here may disrupt PALB2 function or expression[70-71,73].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the PALB2 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 with no conflicts) associated with familial breast cancer (ClinVar, Sep 2020)[74]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in PALB2 have been associated with increased risk of breast cancer, with a cumulative risk estimated at 35% to 40% by age 70[75-77], as well as with elevated risk of pancreatic and ovarian cancer development[78]. Biallelic mutations of PALB2 are associated with Fanconi anemia (FA), a rare autosomal recessive disorder that predisposes patients to a subset of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome, gynecological malignancies, and head and neck tumors[79-81]; frequency estimates suggest an incidence of 3:1,000,000 individuals in Europe and the US, and a heterozygous carrier frequency of 1:181 and 1:300 in the US and Europe, respectively, with slightly higher rates in some groups, such as the Ashkenazi Jewish population (1:89)[80,82]. In the appropriate clinical context, germline testing of PALB2 is recommended.

GENE
GNA13

ALTERATION
K42N - subclonal

TRANSCRIPT ID
NM_006572

CODING SEQUENCE EFFECT
126G>C

VARIANT ALLELE FREQUENCY (% VAF)
5.3%

POTENTIAL TREATMENT STRATEGIES
There are no therapies or clinical trials that address genomic alterations in GNA13. Preclinical studies have shown that activation of G alpha-13 results in activation of Rho GTPase signaling[83-85]. 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
In the TCGA dataset, GNA13 mutation was not observed in any of 507 invasive breast carcinoma cases[14]. Activation of GNA12 and GNA13 in vitro is reported to promote invasion and migration of breast cancer cells[86].

FINDING SUMMARY
GNA13 encodes the guanine nucleotide-binding protein subunit alpha-13 (G alpha-13), one of a family of 16 genes that encode G protein alpha subunits; G alpha-12 and G alpha-13 make up the G12 subfamily[87]. G12 proteins function as modulators or transducers in various transmembrane signaling systems, impacting cell growth and cytoskeleton changes[88]. 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.

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Atezolizumab

Assay findings association

Tumor Mutational Burden
10 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 clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In a retrospective analysis of patients with 17 solid tumor types (comprised of 47% NSCLC, 40% urothelial carcinoma, and 13% encompassing 15 other solid tumors), TMB of 16 Muts/Mb or greater was reported to be associated with an improved ORR to atezolizumab compared to chemotherapy (30% vs. 14%)[11]. As first-line treatment for locally advanced or metastatic triple-negative breast cancer (mTNBC), the addition of atezolizumab to nab-paclitaxel significantly prolonged median PFS (7.2 vs. 5.5 months, HR=0.80) and numerically increased OS (21.0 vs. 18.7 months, HR=0.86) in the placebo-controlled Phase 3 IMpassion130 study[90-91] . Patients with PD-L1-positive tumors (≥1% of tumor-infiltrating immune cells [ICs]) achieved significant PFS (7.5 vs. 5.3 months, HR=0.62) and OS (25.40 vs. 17.98.0 months, HR=0.6771) benefit from added atezolizumab, whereas survival was not improved for patients with PD-L1-negative tumors (OS of 19.7 vs. 19.76 months, HR=1.02)[91-92] . Higher TMB was associated with OS benefit only in the PD-L1-positive population[93]. A Phase 1b study also combining atezolizumab with nab-paclitaxel for patients with mTNBC reported an ORR of 30.0% (6/20; 0 CRs, 6 PRs), a median PFS of 5.1 months, and a median OS of 12.4 months in the second-line or later setting[94]. As single-agent therapy for mTNBC, atezolizumab elicited an ORR of 23.8% (5/21) and a median OS of 17.6 months in the first-line setting and an ORR of 6.4% (6/94) and a median OS of 7.3 months for previously treated patients[95]. PD-L1 positivity (≥1% of ICs) was associated with more benefit from atezolizumab monotherapy (ORR of 12.1% [11/91] vs. 0.0% [0/21], median OS of 10.1 vs. 6.0 months)[95]. In a Phase 1 trial, the triplet combination of atezolizumab, pan-AKT inhibitor ipatasertib, and paclitaxel or nab-paclitaxel for patients with treatment-naive locally advanced TNBC or mTNBC elicited an ORR of 73.1% (19/26), with responses observed independent of PD-L1 or PIK3CA/AKT1/PTEN alteration status[96].

Olaparib

Assay findings association

PALB2
S254fs*3, splice site 3113+1G>A

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

On the basis of clinical evidence in breast, bladder, pancreatic, ovarian, and prostate cancer[53-58,97-99] , PALB2 loss or inactivation may predict sensitivity to PARP inhibitors.

SUPPORTING DATA

The phase 2 TBCRC 048 study for patients with metastatic breast cancer reported an ORR of 82% (9/11) in patients with germline PALB2 mutation treated with single-agent olaparib[100]. Patients with HER2-negative metastatic breast cancer and germline BRCA mutation achieved significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (59.9% vs. 28.8%) on olaparib compared with standard chemotherapy (capecitabine, eribulin, or vinorelbine) in a Phase 3 study[101]. Phase 1 trials of olaparib plus chemotherapy for patients with triple-negative breast cancer (TNBC) reported ORRs of 37% to 38%[102-103] . A small Phase 1 trial reported a 20% ORR (1/5) for patients with breast cancer and wild-type germline BRCA status following combination treatment with olaparib and buparlisib[104]. A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel (DOP) to chemotherapy alone reported pathologic complete response (pCR) for 37% versus 22% of patients with HER2-negative breast cancer, 47% versus 27% of patients with TNBC, and 28% versus 14% of patients with HR-positive HER2-negative breast cancer[105].

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Pembrolizumab

Assay findings association

Tumor Mutational Burden
10 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-H; ≥10 Muts/Mb), microsatellite instability-high (MSI-H), 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-H or dMMR, or triple-negative breast cancer (TNBC) with PD-L1 expression (CPS≥10). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In the Phase 2 KEYNOTE 158 multi-solid tumor trial, treatment with the PD-1 inhibitor pembrolizumab led to improved ORR for patients with TMB of 10 Muts/Mb or higher compared those with TMB < 10 Muts/Mb (28.3% [34/120] vs. 6.5% [41/635])[10]. In the KEYNOTE 028/012 pan-solid tumor trials, a similar improvement in ORR was reported for patients with >103 non-synoymous mutations/exome (~ equivalency >8 Muts/Mb as measured by this assay) compared to those with <103 non-synoymous mutations/exome (30.6% [11/36] vs. 6.5% [5/77])[4]. Patients with metastatic breast cancer, TMB of at least 9 Muts/Mb, and no remaining standard treatment options achieved an ORR of 21% (6/28 PRs), median PFS of 10.6 weeks, and median OS of 31.6 weeks with pembrolizumab in the Phase 2 basket TAPUR study[106]. Out of 4 patients with hypermutated breast cancer (TMB values of 13.3, 93.8, and 21.3 Muts/Mb) treated with pembrolizumab-based regimens, 3 experienced an objective response[13]. Exploratory biomarker analysis of the Phase 2 KEYNOTE-086 study for patients with triple-negative breast cancer showed a significant association between TMB and response to pembrolizumab in the combined cohort (p=0.007)[107]. The Phase 3 randomized KEYNOTE-119 study of pembrolizumab versus chemotherapy for previously treated patients with metastatic triple-negative breast cancer (TNBC) reported no significant difference in median PFS (mPFS; 2.1 vs. 3.3 months, HR=1.60) or median OS (9.9 vs. 10.8 months, HR=0.97)[108]. In the Phase 2 KEYNOTE-086 study, pembrolizumab monotherapy for patients with previously untreated PD-L1-positive metastatic TNBC achieved an ORR of 21.4%, mPFS of 2.1 months, and median OS of 18 months[109]. The Phase 3 KEYNOTE-522 randomized study of chemotherapy with pembrolizumab or placebo as both neoadjuvant and adjuvant treatment for patients with early TNBC reported a significant increase in pathological CRs for the pembrolizumab group (64.8% vs. 51.2%, p<0.001)[110]. In the randomized Phase 3 KEYNOTE-355 study for patients with untreated metastatic TNBC, pembrolizumab plus chemotherapy significantly improved mPFS for patients with PD-L1 combined positive score (CPS) ≥10 versus placebo plus chemotherapy (9.7 vs. 5.6 months, HR=0.65); improvement to mPFS did not reach pre-specified statistical significance for patients with PD-L1 CPS <1 (7.6 vs. 5.6 months, HR=0.74)[111]. The Phase 2 I-SPY 2 randomized trial of chemotherapy with or without pembrolizumab reported pathologic CRs for 60% versus 22% of patients with high-risk TNBC and 30% versus 13% for patients with hormone receptor-positive (HR+), HER2– high-risk breast cancer[112]. A Phase 2 study of pembrolizumab with the PARP inhibitor niraparib for patients with metastatic TNBC reported an ORR of 21.3% (5 CRs, 5 PRs, out of 47 patients)[113]. A Phase 2 study of pembrolizumab with radiation therapy for patients with metastatic TNBC reported 33.3% CR (3/9)[114]. A Phase 1b/2 study of pembrolizumab with eribulin mesylate for previously treated patients with metastatic TNBC reported an ORR of 25.6%[115]. In 2 Phase 1b trials for heavily pretreated patients with advanced HR+, HER2– PD-L1-positive metastatic breast cancer, pembrolizumab led to an ORR of 12% (3/25 PRs)[116] and to an ORR of 14.3% (4/28 PRs) when combined with abemaciclib[117]. The triplet combination of pembrolizumab, abemaciclib, and anastrozole for postmenopausal patients with HR+, HER2– metastatic breast cancer studied in a Phase 1b trial reported an ORR of 23.1% (6/26) with 1 CR; however, this ORR is lower than previously reported for patients treated with the abemaciclib plus nonsteroidal aromatase inhibitor combination[118].

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Talazoparib

Assay findings association

PALB2
S254fs*3, splice site 3113+1G>A

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

On the basis of clinical benefit in breast, bladder, pancreatic, ovarian, and prostate cancer[53,56-58,98-99], PALB2 inactivation may predict sensitivity to PARP inhibitors. Talazoparib achieved objective responses (3/5 PRs) or SD with tumor shrinkage (2/5) for all of 5 patients with advanced breast cancer and germline PALB2 alterations in a prospective study[57].

SUPPORTING DATA

In the Phase 3 EMBRACA trial, patients with HER2-negative advanced breast cancer and germline BRCA mutations achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (63% vs. 27%), and improved quality of life on talazoparib compared with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)[119-120]. Clinical benefit from talazoparib was observed for patients with either triple-negative or hormone receptor-positive (HR+) breast cancer, and for those with CNS metastases[119]. Final OS analysis showed that talazoparib did not significantly improve OS compared with chemotherapy (median OS [mOS] 19.3 vs. 19.5 months, HR=0.85) but did significantly delay definitive clinically meaningful deterioration in global health status/quality of life[121]. Retrospective genomic analysis showed that MYC amplification was associated with significantly shorter mOS for patients with triple-negative cancer treated with talazoparib, but not for those treated with chemotherapy; in contrast, for patients with HR+ cancer, MYC amplification was associated with shorter mOS for the chemotherapy treatment group, but not for the talazoparib treatment group[122]. The efficacy of single-agent talazoparib for the treatment of BRCA-mutated advanced breast cancer was also demonstrated in earlier-phase studies, which reported ORRs of 21%-50%[99,123]. As neoadjuvant treatment for BRCA-mutated HER2-negative breast cancer, talazoparib led to a pathologic complete response (pCR) for 53% (10/19) of patients[124]. In the Phase 2 I-SPY2 trial, talazoparib with synergy-dosed irinotecan (TI) for patients with early stage, high-risk HER2-negative breast cancer reported fewer Grade 3/4 adverse events compared with the chemotherapy control arm (paclitaxel with doxorubicin and cyclophosphamide [AC]), although a similar pCR rate was observed[125]. Notably, 6/10 patients with germline BRCA mutations achieved a pCR with TI treatment[125]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, those with HER2-negative advanced breast cancer experienced an ORR of 31% (4/13 PRs), with responses observed for 3 patients with germline PALB2 mutations and for 1 patient with germline CHEK2 and FANCA mutations as well as somatic PTEN mutation; 3 additional patients with germline PALB2 or somatic ATR or PTEN alterations had SD ≥6 months[57].

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Avelumab

Assay findings association

Tumor Mutational Burden
10 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 clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In metastatic breast cancer, an unconfirmed objective response rate of 5.4% (9/168) and a disease control rate of 29.2% (49/168) were reported for avelumab monotherapy; partial response was seen in 8.8% (5/57) of triple-negative patients[126]. The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[127], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[128], urothelial carcinoma[129], mesothelioma[130], ovarian carcinoma[131], and breast cancer[126], and from avelumab combined with axitinib in renal cell carcinoma[132]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[126-127,131] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[133-135] .

Cemiplimab

Assay findings association

Tumor Mutational Burden
10 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 locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of breast cancer are limited (PubMed, Aug 2020). Cemiplimab has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[136]. The Phase 3 EMPOWER-Lung 1 trial for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50% reported that cemiplimab is associated with improved PFS (8.2 vs. 5.7 months), OS (not reached vs. 14.2 months), and ORR (37% vs. 21%) compared with chemotherapy[137].

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Durvalumab

Assay findings association

Tumor Mutational Burden
10 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 urothelial carcinoma, 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 clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel (DOP) to chemotherapy alone reported pathologic complete responses (pCR) in 37% versus 22% for all patients with HER2-negative breast cancer, 47% versus 27% for patients with triple-negative breast cancer (TNBC), and 28% versus 14% for patients with HR-positive HER2-negative breast cancer[105]. In a Phase 2 study of durvalumab in combination with tremelimumab, patients with TNBC achieved an ORR of 43% (3/7) and patients with PD-L1-unselected estrogen receptor-positive metastatic breast cancer (MBC) achieved an ORR of 17% (3/18)[138]. In a randomized Phase 2 trial of durvalumab plus standard neoadjuvant chemotherapy for 174 patients with TNBC, durvalumab provided higher pathological complete response (pCR) before (61% vs. 41%, p=0.03) and after neo-adjuvant chemotherapy (53% vs. 44%, p=0.28) compared with placebo[139]. A Phase 1b trial of durvalumab in combination with trastuzumab for 14 patients with HER2-positive and PD-L1 negative MBC heavily pretreated with chemotherapy and anti-HER2 antibodies reported no significant clinical activity[140]. In a Phase 1 trial, 2 patients with TNBC achieved stable disease lasting 7 to 14.5 months in response to a combination of durvalumab and olaparib[141].

Niraparib

Assay findings association

PALB2
S254fs*3, splice site 3113+1G>A

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

On the basis of clinical evidence in breast, bladder, pancreatic, ovarian, and prostate cancer[53-58,97-99] , PALB2 loss or inactivation may predict sensitivity to PARP inhibitors.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/4 patients with breast cancer and BRCA1/2 mutations experienced a PR[142]. An open label study combining PD-1 inhibitor pembrolizumab with niraparib for patients with TNBC reported an ORR of 21% and DCR of 49%; ORR and DCR for patients with BRCA alterations were 47% and 80%, respectively, with 2 CRs, 5 PRs, 5 SDs and mPFS of 8.3 months[113].

Nivolumab

Assay findings association

Tumor Mutational Burden
10 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), and esophageal 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 clinical data across solid tumors[2-4,11,89] , 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 of patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

A case study reported a patient with ER-positive, HER2-negative metastatic breast ductal carcinoma harboring high TMB (40 muts/Mb) who experienced a CR lasting >26 months to nivolumab in combination with capecitabine[16]. A Phase 2 randomized trial of nivolumab after induction with irradiation or low-dose chemotherapy for the treatment of metastatic triple-negative breast cancer reported an objective response rate of 22%, including 4% (2/50) complete responses, and a 10.9-month median duration of response[143].

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Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
10 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[5-6,144] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

Clinical data on the efficacy of nivolumab combined with ipilimumab for the treatment of breast cancer are limited (PubMed, Dec 2020). Combination treatment with nivolumab plus the CTLA-4 inhibitor ipilimumab has achieved efficacy in melanoma (up to 61% ORR; mOS >60 months for the combination vs. 37 months for nivolumab monotherapy)[145-148] , NSCLC (17 months mOS)[149], MSI-High CRC (64% ORR)[150], RCC (42% ORR)[151-152] , SCLC (19–25% ORR)[130,153] , urothelial carcinoma (38% ORR in unselected patients; 58% ORR in patients with ≥1% tumor PD-L1 expression)[154], and other solid tumors.

Rucaparib

Assay findings association

PALB2
S254fs*3, splice site 3113+1G>A

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

On the basis of clinical evidence in breast, bladder, pancreatic, ovarian, and prostate cancer[53-58,97-99] , PALB2 loss or inactivation may predict sensitivity to PARP inhibitors.

SUPPORTING DATA

In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and BRCA1/2 mutations, no objective responses were reported in breast cancer patients[155]. However, 39% (9/23) of evaluable patients with breast cancer achieved stable disease lasting 12 weeks or more[155]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 1 patient with breast cancer and a BRCA mutation given the recommended Phase 2 dose reported an objective response[156].

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 Donna Ferguson, M.D. | 02 February 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

Tumor Mutational Burden

RESULT

10 Muts/Mb

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.

NCT03498716

PHASE 3

A Study Comparing Atezolizumab (Anti PD-L1 Antibody) In Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone In Patients With Operable Triple-Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Arequipa (Peru), San Miguel de Tucuman (Argentina), La Rioja (Argentina), Cordoba (Argentina), Rosario (Argentina), Ijui (Brazil), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Jau (Brazil)

NCT04148911

PHASE 3

A Study of Atezolizumab (Tecentriq) Plus Nab-Paclitaxel or Paclitaxel in the Treatment of Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Santiago (Chile), Rosario (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), Buenos Aires (Argentina), Oaxaca (Mexico), Distrito Federal (Mexico), Ciudad de México (Mexico), Chihuahua (Mexico), Lisboa (Portugal)

NCT04249167

PHASE NULL

Cryoablation, Atezolizumab/Nab-paclitaxel for Locally Advanced or Metastatic Triple Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Florida

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Cali (Colombia), Medellin (Colombia), La Serena (Chile), Monteria (Colombia), Vina del Mar (Chile), Santiago (Chile), Barranquilla (Colombia), Temuco (Chile), Florida, Texas

NCT03725059

PHASE 3

Study of Pembrolizumab (MK-3475) Versus Placebo in Combination With Neoadjuvant Chemotherapy & Adjuvant Endocrine Therapy in the Treatment of Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) Breast Cancer (MK-3475-756/KEYNOTE-756)

TARGETS
PD-1

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Barranquilla (Colombia), Ijui (Brazil), Goiania (Brazil), Porto Alegre (Brazil), Itajai (Brazil), Florianopolis (Brazil)

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NCT04109066

PHASE 3

Study of Nivolumab Versus Placebo in Participants With High-Risk Breast Cancer

TARGETS
PD-1

LOCATIONS: Cali (Colombia), Colombia (Colombia), Bogota (Colombia), Rionegro, Antioquia (Colombia), La Serena (Chile), Floridablanca (Colombia), Monteria (Colombia), Vina del Mar (Chile), Santiago de Chile (Chile), Santiago Region Metropolitana (Chile)

NCT03371017

PHASE 3

A Study of the Efficacy and Safety of Atezolizumab Plus Chemotherapy for Patients With Early Relapsing Recurrent Triple-Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Panama (Panama), Rosario (Argentina), Goiania (Brazil), Passo Fundo (Brazil), Buenos Aires (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), Sao Paulo (Brazil), La Habana (Cuba), Florida

NCT03369223

PHASE 1/2

An Investigational Immunotherapy Study of BMS-986249 Alone and in Combination With Nivolumab in Solid Cancers That Are Advanced or Have Spread

TARGETS
CTLA-4, PD-1

LOCATIONS: Santiago (Chile), Buenos Aires (Argentina), Florida, Texas, South Carolina, Virginia

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Santiago (Chile), Toronto (Canada), Montreal (Canada), Sevilla (Spain), Valencia (Spain), San Sebastian (Spain), Bordeaux (France), Hospitalet de Llobregat (Spain), Barcelona (Spain), Villejuif (France)

NCT03310957

PHASE 1/2

Safety and Efficacy of SGN-LIV1A Plus Pembrolizumab for Patients With Locally-Advanced or Metastatic Triple-Negative Breast Cancer

TARGETS
PD-1, LIV-1

LOCATIONS: Florida, Texas, Georgia, Alabama, Virginia, Maryland

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GENE
PALB2

RATIONALE
Tumors with PALB2 mutation or loss may be sensitive to PARP inhibitors.

ALTERATION
S254fs*3, splice site 3113+1G>A

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), Cali (Colombia), Medellin (Colombia), Bucaramanga (Colombia), Barranquilla (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina), Guatemala (Guatemala)

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Cali (Colombia), Medellin (Colombia), La Serena (Chile), Monteria (Colombia), Vina del Mar (Chile), Santiago (Chile), Barranquilla (Colombia), Temuco (Chile), Florida, Texas

NCT03598257

PHASE 2

Radiation Therapy With or Without Olaparib in Treating Patients With Inflammatory Breast Cancer

TARGETS
PARP

LOCATIONS: San Juan (Puerto Rico), Florida, Louisiana, Georgia, Texas, South Carolina

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, Oklahoma, Pennsylvania, Indiana

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ORDERED TEST # ORD-1002477-01

CLINICAL TRIALS

NCT04171700

PHASE 2

A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes

TARGETS
PARP

LOCATIONS: Florida, Tennessee, Texas, Oklahoma, Pennsylvania, New York

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

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Texas, Tennessee, Massachusetts

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Texas, Connecticut, Newcastle upon Tyne (United Kingdom)

NCT02286687

PHASE 2

Phase II Study of BMN 673

TARGETS
PARP

LOCATIONS: Texas

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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.

ASXL1
A746G

AXIN1
A526V

CASP8
D496V

CD79A
P77H

CDK12
G239A

EP300
R1646K

ESR1
S236G

HRAS
R169W

INPP4B
M307T

KMT2A (MLL)
A53V

MLL2
Q3612_H3613insQ

POLD1
L967R and V187M

SMARCA4
H1241_R1244del

TSC1
K587R

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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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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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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. Observed TMB is dependent on characteristics

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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.

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 with no conflicts), 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 *BAP1, BRCA1, BRCA2, BRIP1, 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.

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 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 2.2.0

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The median exon coverage for this sample is 1,050x

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