FOUNDATIONONE®CDx

PATIENT
Chien, Ching I

TUMOR TYPE
Unspecified primary endometrioid carcinoma

COUNTRY CODE
TW

REPORT DATE
16 Jun 2023

ORDERED TEST #
ORD-1648396-01

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 Unspecified primary endometrioid carcinoma
NAME Chien, Ching I
DATE OF BIRTH 08 November 1971
SEX Female
MEDICAL RECORD # 21088846

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Pelvis
SPECIMEN ID S112-66324A (PF23077)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 28 March 2023
SPECIMEN RECEIVED 09 June 2023

Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - 14 Muts/Mb
Homologous Recombination status - HRD Not Detected
Loss of Heterozygosity score - 2.6%

Genomic Findings

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

ARID1A G324fs*39
ATM S214fs*40
PIK3R1 Y452_N453>H, W597fs*2, E601fs*57
PTEN R130P, T319fs*1
CIC L571fs*157, P1248fs*54
CTCF A175fs*3
EED I251fs*11
MSH6 F1088fs*2
SMARCA4 P109fs*194
SOX9 V306fs*77

2 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Dostarlimab** (p. 13), **Pembrolizumab** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 20)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***ATM* S214fs*40** (p. 7)

BIOMARKER FINDINGS

Microsatellite status - MSI-High

10 Trials see p. 20

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	
Dostarlimab	2A
Pembrolizumab	2A

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Atezolizumab
Avelumab
Cemiplimab
Durvalumab
Durvalumab + Tremelimumab
Nivolumab
Nivolumab + Ipilimumab
Retifanlimab

Electronically signed by Erik Williams, M.D. | 16 June 2023
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

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 14 Muts/Mb	Pembrolizumab 2A	Atezolizumab
	Dostarlimab	Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
		Nivolumab + Ipilimumab
10 Trials see p. 22		Retifanlimab
Homologous Recombination status - HRD Not Detected	HRD Not Detected defined as absence of deleterious *BRCA1/2* alteration and LOH score < 16% or Cannot Be Determined (Coleman et al., 2017; 28916367).	
Loss of Heterozygosity score - 2.6%	**No therapies or clinical trials.** See Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***ARID1A* -** G324fs*39	none	none
10 Trials see p. 24		
***ATM* -** S214fs*40	none	none
10 Trials see p. 26		
***PIK3R1* -** Y452_N453>H, W597fs*2, E601fs*57	none	none
5 Trials see p. 28		
***PTEN* -** R130P, T319fs*1	none	none
10 Trials see p. 29		

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.

***ATM* -** S214fs*40 ..... p. 7

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 TRIAL 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.

BIOMARKER

Microsatellite status

RESULT
MSI-High

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), retifanlimab, and pembrolizumab[3-9], as well as PD-L1-targeting agents atezolizumab, avelumab, and durvalumab (alone or in combination with tremelimumab)[10-11].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples[12-13], including 3.8% (1/26) of ovarian endometrioid adenocarcinomas[14], and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)[15]. No association of MSI-H with stage or survival was found in patients with ovarian cancer[12,16].

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[17]. 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[17-19]. 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[20-22]. 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[17,19,21-22].

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[17], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[23]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[23-25] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[26-28]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
14 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[29-31], anti-PD-1 therapies[29-32], and combination nivolumab and ipilimumab[33-38]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[29-32,39-43]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[39]; similar findings were observed in the KEYNOTE 028 and 012 trials[32]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[43]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[44]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[42]. Similarly, 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[45] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[30].

FREQUENCY & PROGNOSIS

Ovarian carcinomas, including peritoneal and Fallopian tube carcinomas, harbor a median TMB of 2.7-3.6 mutations per megabase (muts/Mb) depending upon subtype, and up to 2.1% of cases have high TMB (>20 muts/Mb)[46]. In a study of high grade serous ovarian cancer, homologous recombination (HR)-deficient tumors, which comprised ~50% of all samples, harbored a higher neoantigen load compared to HR-proficient tumors; higher neoantigen load was associated with longer OS but not disease free survival[47].

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[48-49] and cigarette smoke in lung cancer[8,50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[53-57], and microsatellite instability (MSI)[53,56-57]. 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[30-32,39].

BIOMARKER

Loss of Heterozygosity score

RESULT
2.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[58-59]. In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, rucaparib elicited significantly longer median PFS (7.2 vs. 5.0 months, HR=0.51) and improved ORR (33.3% vs. 9.6%, p=0.0003) for patients with LOH score ≥ 16%[59]. In the maintenance setting in platinum-sensitive, BRCA1/2 wild-type patients, rucaparib was superior to placebo in both the LOH score ≥ 16% (median PFS, 9.7 vs. 5.4 months; HR=0.44) and LOH score < 16% (median PFS, 6.7 vs. 5.4 months; HR=0.58) cohorts[58]. Similar results have been reported for maintenance treatment with niraparib in ovarian cancer[60] when using a different measure of HRD that includes genomic LOH[61-62]. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer[63-65].

FREQUENCY & PROGNOSIS

In a study of more than 4,000 ovarian, Fallopian tube, or peritoneal cancer samples, genomic LOH score ≥ 16% was identified in 24.2% of BRCA1/2 wild-type cases, deleterious BRCA1/2 mutation was identified in an additional 17.2% of cases, and the remaining 58.7% of cases had LOH score < 16% and were BRCA1/2 wild-type[66]. Among the histological subtypes, LOH score ≥ 16% or BRCA1/2 mutation was reported in 42.4% of serous carcinomas, 37.6% of endometrioid carcinomas, 23.5% of carcinosarcomas, 20.6% of neuroendocrine carcinomas, 13.6% of clear cell carcinomas, and 8.1% of mucinous carcinomas; in BRCA1/2 wild-type samples, the median LOH score was significantly higher in serous as compared with non-serous cases[66]. In ovarian carcinoma, the median LOH score is significantly higher for BRCA1/2-mutated cases than BRCA1/2 wild-type cases (22.2% vs. 9.8%)[66], and mutation or methylation of BRCA1, BRCA2, or RAD51C has been reported to be enriched in cases with increased genomic LOH[63,67]. One study reported no association between LOH and either tumor stage or grade in ovarian serous carcinoma[68]. In patients with high-grade serous ovarian carcinoma, the frequency of LOH has been reported to increase significantly with age[69].

FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele[59]; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)[63,67,70-71]. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1[70-73]. This sample harbors a genomic LOH score below levels that have been associated with improved rates of clinical benefit from treatment with the PARP inhibitor rucaparib in patients with platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma[59]. However, patients with lower genomic LOH have also responded to rucaparib, and this type of LOH score does not preclude benefit from PARP inhibitors[58-59].

GENE
ARID1A

ALTERATION
G324fs*39

HGVS VARIANT
NM_006015.4:c.971del (p.G324Afs*39)

VARIANT CHROMOSOMAL POSITION
chr1:27023860-27023861

VARIANT ALLELE FREQUENCY (% VAF)
34.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[74]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[75]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[76]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[77]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[78-79]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[80]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[81-83]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[84]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[85-86] and to 5-fluorouracil in CRC cell lines[87].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[88-96]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[14,84,97-99], CRC[84,100-102], and gastric cancer[84,103-107]. Several studies have reported no correlation between ARID1A loss and clinicopathological parameters in ovarian clear cell or endometrioid carcinomas or other endometrial cancers[108-111], whereas others suggest that ARID1A loss is a negative prognostic factor[86,112].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[92,106,113-119]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[92,104,114-115,120], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
ATM

ALTERATION
S214fs*40

HGVS VARIANT
NM_000051.3:c.640dup (p.S214Ffs*40)

VARIANT CHROMOSOMAL POSITION
chr11:108114816

VARIANT ALLELE FREQUENCY (% VAF)
32.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[121-122]. Clinical responses have been reported for patients with ATM-mutated prostate cancer treated with PARP inhibitors[123-125] and PARP inhibitors have shown limited clinical benefit for patients with other ATM-mutated solid tumors including pancreatic cancer[126-127] , colorectal cancer[128], papillary renal cell carcinoma[129], ovarian cancer[130], small cell bowel cancer,[127], and biliary tract cancer[131]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[132] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[133] harbored ATM inactivation or protein loss. In a Phase 2 study of a combination of the ATR inhibitor ceralasertib and durvalumab for patients with advanced gastric cancer, objective responses (ORs) were experienced by 50% (4/8) of patients with loss of ATM expression, compared with 14% (3/21) patients with intact ATM[134]. Studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[135-137] and hematologic malignancies[135,138] 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[139].

— Nontargeted Approaches —

Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D have been reported to be predictive for sensitivity to platinum agents and improved OS in Stage 2-4 ovarian, fallopian tube, and peritoneal carcinomas (p=0.0006)[140].

FREQUENCY & PROGNOSIS

ATM mutations have been reported in up to 1.3% of ovarian serous carcinoma samples analyzed[72]. In another study of patients with peritoneal, Fallopian tube, or ovarian carcinoma, somatic loss-of-function mutations in ATM have been found in 3/367 cases[140]. The homologous recombination pathway has been reported to be disrupted in over 50% of high-grade serous ovarian cancer cases analyzed, including ATM or ATR mutations in 2% of tumors sampled[72,141]. A lack of ATM protein expression was reported in 11.3% of ovarian serous carcinomas, but this ATM deficiency was not significantly correlated with clinicopathological features[142]. ATM protein expression was found in 46.2% (79/171) of sporadic ovarian carcinomas analyzed in one study; the authors suggest that this may be compensatory expression in homologous recombination deficient cancer cells[143]. In one study, high expression of ATM protein significantly correlated with poor progression-free survival in ovarian serous cystadenocarcinomas[144].

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[145]. Loss of functional ATM promotes tumorigenesis[146]. Alterations such as seen here may disrupt ATM function or expression[147-149].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the ATM 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 ataxia-telangiectasia syndrome (ClinVar, Apr 2023)[150]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. ATM mutation carriers have increased cancer risk, with carriers assigned female at birth displaying a 38% lifetime risk of breast cancer[151]. 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[152]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[145,152]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[152]. 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[153-158]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[157,159-160]. 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

PIK3R1

ALTERATION
Y452_N453>H, W597fs*2, E601fs*57

HGVS VARIANT
NM_181523.3:c.1354_1357delinsC (p.Y452_N453delinsH), NM_181523.3:c.1789_1796del (p.W597Qfs*2), NM_181523.3:c.1801_1813del (p.E601Tfs*57)

VARIANT CHROMOSOMAL POSITION
chr5:67589591-67589594, chr5:67591289-67591297, chr5:67591302-67591315

VARIANT ALLELE FREQUENCY (% VAF)
32.6%, 28.2%, 25.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical[161-162] and preclinical[163-164] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[161], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[165]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[164,166-169] or AKT[170-171]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[172].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[53], glioblastoma (GBM; 11%)[173], uterine carcinosarcoma (11%)(cBioPortal, Jan 2023)[89-90], and lower grade glioma (5%)[174]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[175-177], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[175]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[178] and metastasis-free survival in breast cancer[179]. PIK3R1 expression is not associated with OS in neuroendocrine tumors[180].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[181]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[182-185], promote tumorigenesis[163,170,182], and promote hyperplasia in the context of PTEN-deficiency[186]. Alterations such as seen here may disrupt PIK3R1 function or expression[164,171-172,176-177,187-196].

GENE
PTEN

ALTERATION
R130P, T319fs*1

HGVS VARIANT
NM_000314.4:c.389G>C (p.R130P),
NM_000314.4:c.955_958del (p.T319*)

VARIANT CHROMOSOMAL POSITION
chr10:89692905, chr10:89720798-89720802

VARIANT ALLELE FREQUENCY (% VAF)
36.9%, 21.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[197-200]. While most clinical studies of PTEN-deficient cancers have not observed efficacy for inhibitors of the PI3K-AKT-mTOR pathway, clinical benefit has been reported in limited studies in prostate cancer[201-204], renal cell carcinoma (RCC)[205], breast cancer[206-208], and colorectal cancer (CRC)[209]. In the TAPUR study, the mTOR inhibitor temsirolimus met the prespecified threshold of activity for the cohort of solid tumors with PTEN mutations (ORR 7.4%, DCR 26%, n=27)[210]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[211-215], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[216], ovarian cancer[217], uterine leiomyosarcoma[218], and endometrial cancer[215] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[219-220]. In a Phase 1 study of patients treated with PARP and AKT inhibitors olaparib and capivasertib, two patients with PTEN-mutated ovarian cancer and a patient with PTEN-mutated endometrial cancer achieved clinical benefit (CR, PR, or SD >4 months)[221].

FREQUENCY & PROGNOSIS

PTEN mutations have been reported in <1% of ovarian serous carcinoma cases[72], but may be more common in other subtypes, including endometrioid, with smaller studies identifying mutations 17-34% of cases[222-224]. Loss of heterozygosity at the chromosomal region including PTEN has been reported in 31% (22/72) of epithelial ovarian tumors analyzed, with an incidence of 43% (13/30) in endometrioid tumors and 28% (7/25) in serous tumors and lower incidences in other histological subtypes[222]. Reduced PTEN expression has been reported in 55% (26/47) to 69% (104/151) of ovarian epithelial cancers[225-226]. In a study of endometriosis-associated ovarian cancers, loss of PTEN expression has been found in 37% (29/79) of cases[227]. Reduced PTEN expression has been suggested to be associated with poor prognosis in ovarian cancer[225-226,228].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[198]. Alterations such as seen here may disrupt PTEN function or expression[229-270].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN 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 hamartoma tumor syndrome (ClinVar, Apr 2023)[150]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[271-272]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[271,273]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[271]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
CIC

ALTERATION
L571fs*157, P1248fs*54

HGVS VARIANT
NM_015125.4:c.1711del (p.L571Yfs*157),
NM_015125.4:c.3743del (p.P1248Hfs*54)

VARIANT CHROMOSOMAL POSITION
chr19:42794626-42794627, chr19:42797375-42797376

VARIANT ALLELE FREQUENCY (% VAF)
31.8%, 30.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

CIC mutations have been described in various solid tumors, including 1–10% of sequenced gastric, endometrial, and colorectal carcinomas and melanoma tumors (cBioPortal, COSMIC, Jan 2023)[88-90], although the consequences of CIC mutations in these tumor types have not been studied. CIC mutations have been observed in 58–69% of oligodendrogliomas but are less common in other gliomas, such as astrocytoma or oligoastrocytoma[274-276]. Published data investigating the prognostic implications of CIC alterations are generally limited (PubMed, Jun 2023). Conflicting data have been reported regarding the prognostic significance of CIC mutation in oligodendroglioma[275,277-278].

FINDING SUMMARY

CIC encodes a transcriptional repressor that plays a role in central nervous system (CNS) development[279]. CIC inactivation has been reported in various malignancies, and is highly recurrent in oligodendroglioma[274-275].

GENE
CTCF

ALTERATION
A175fs*3

HGVS VARIANT
NM_001191022.1:c.502_523dup (p.A175Efs*3)

VARIANT CHROMOSOMAL POSITION
chr16:67660585

VARIANT ALLELE FREQUENCY (% VAF)
30.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Somatic mutations in CTCF are infrequently reported in most cancers, but have been observed more commonly (24%) in uterine corpus endometrial carcinoma (cBioPortal, 2023)[89-90]; nearly half of the observed mutations were truncating, suggesting a tumor suppressor role for CTCF in this disease. In addition, CTCF has been found to act as a tumor suppressor in breast cancer cell line studies[280-281].

FINDING SUMMARY

CTCF encodes an 11-zinc-finger protein that is implicated in various regulatory roles, including gene activation and repression, imprinting, insulation, methylation, and X chromosome inactivation[282]. CTCF plays a role in transcriptional regulation of a number of key cancer-associated genes, including the oncogene MYC[283] and tumor suppressor TP53[284], via maintenance of local DNA methylation status. Decreased expression levels of CTCF and/or BORIS, another 11-zinc-finger transcriptional regulator, were reported to be closely associated with global DNA methylation variability and decreased OS in epithelial ovarian cancer[285-286].

GENE
EED

ALTERATION
I251fs*11

HGVS VARIANT
NM_003797.2:c.751dup (p.I251Nfs*11)

VARIANT CHROMOSOMAL POSITION
chr11:85977143

VARIANT ALLELE FREQUENCY (% VAF)
39.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available that target EED inactivation. Strategies are being developed to target EED in cancers with excessive PRC2 activation, such as inhibitors that disrupt EED-histone binding[287] or prevent PRC2 activation[288-292].

FREQUENCY & PROGNOSIS

EED alterations, including frameshift or missense mutations (2%), heterozygous deletions (3-4%), homozygous deletions (10-12%), and concurrent heterozygous deletion and mutation (2-25%), have been frequently observed in malignant peripheral nerve sheath tumors (MPNSTs)[293-296]. In other tumor types, EED alterations have been reported with the highest incidence in lung adenocarcinoma (6.1%)[297], prostate adenocarcinoma (5.1%)[298], endometrial carcinoma (5%)[53], bladder carcinoma (4.7%)[299], head and neck squamous cell carcinoma (HNSCC) (4.7%)[300], pancreatic intraductal tubulopapillary neoplasm (4.5%, 1/22)[301], and myelodysplastic syndrome (MDS) (3.1%)[302]. Studies have reported no association of EED expression levels with OS for patients with soft tissue sarcoma[303-304]. In contrast, EED overexpression was associated with aggressive subtypes of B- and T-/natural killer-cell neoplasms, compared with indolent subtypes or normal tissue[305].

FINDING SUMMARY

EED encodes a core subunit of the PRC2/EED-EZH2-SUZ12 complex, which methylates histones on DNA to repress transcription and expression of target genes[306-310]. The role of PRC2 in cancer is complex, and the catalytic component EZH2 has been described as both an oncogene and tumor suppressor in different contexts[311-312]. However, the majority of described EED alterations have loss of function effects[313].

GENE
MSH6

ALTERATION
F1088fs*2

HGVS VARIANT
NM_000179.2:c.3261del (p.F1088Sfs*2)

VARIANT CHROMOSOMAL POSITION
chr2:48030639-48030640

VARIANT ALLELE FREQUENCY (% VAF)
9.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Numerous studies in various cancer types have shown that MSH6 loss or inactivation is associated with MSI and increased mutation burden[18,56,314-317]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[7,318] and nivolumab[6]. Higher mutation burden was also reported to be associated with response to pembrolizumab[8]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[319], potential biomarkers of response to PD-1 targeted immunotherapies. Therefore, inactivation of MSH6 may confer sensitivity to anti-PD-1 immune checkpoint inhibitors.

FREQUENCY & PROGNOSIS

In the TCGA ovarian serous cystadenocarcinoma dataset, MSH6 mutations were found in <1.0% of patients, but no MSH6 losses or rearrangements were reported[72]. The risk of ovarian cancer associated with mutations in MSH6 (approximately 1%) has been reported to be lower than that associated with mutations in MLH1 or MSH2 (12% and 16%, respectively)[320].

FINDING SUMMARY

MSH6 encodes MutS homolog 6 protein, a member of the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[18]. Alterations such as seen here may disrupt MSH6 function or expression[321-326].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MSH6 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 Lynch syndrome (ClinVar, Apr 2023)[150]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in MSH6 are associated with both "typical" and "atypical" forms of autosomal dominant Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which accounts for 1-7% of all colorectal cancers[26]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[327]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[25]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[26-28]. Biallelic germline mutation of MSH6 has been shown to account for 20% of cases of the very rare syndrome Constitutional Mismatch Repair Deficiency (CMMRD), which is characterized by a 95% incidence rate of childhood onset lymphoma, leukemia and brain tumors, followed by early-onset colorectal cancer[328-332]. Given the association between MSH6 and these inherited syndromes, in the appropriate clinical context, germline testing of MSH6 is recommended.

GENE
SMARCA4

ALTERATION
P109fs*194

HGVS VARIANT
NM_003072.3:c.326del (p.P109Rfs*194)

VARIANT CHROMOSOMAL POSITION
chr19:11096047-11096048

VARIANT ALLELE FREQUENCY (% VAF)
34.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available that target genomic alterations in SMARCA4; however, clinical benefit to targeted agents has been observed for patients with certain SMARCA4-deficient tumor types. Based on clinical and preclinical data, patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may derive benefit from EZH2 inhibitors such as tazemetostat[333] or CDK4/6 inhibitors such as abemaciclib[334-336]. For patients with SMARCA4-deficient malignant rhabdoid tumors and thoracic undifferentiated tumors, responses have been observed following treatment with anti-PD-1[337] or anti-PD-L1 therapies[338-340].

FREQUENCY & PROGNOSIS

SMARCA4 mutations have been reported in 1.5% of ovarian serous carcinoma samples analyzed in COSMIC (Oct 2022)[88]. Mutation or loss of SMARCA4 has been shown to be a defining molecular characteristic of small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)[341-344], similar to malignant rhabdoid tumors (MRT), leading to the suggestion that treatment regimens used for MRT may be applicable for patients with SCCOHT[342]. SMARCA4 mutation or loss has been reported in 83-94% of SCCOHT tumors, and both germline and somatic alterations have been reported[342-347]. Several studies have shown loss of BRG1 expression due to SMARCA4 gene mutations in SCCOHT samples[348], compared with other types of ovarian clear cell carcinomas, which generally retain BRG1 expression[82,344]. In one study of 3000 primary gynecological tumor samples, loss of SMARCA4 expression was found in 91% (42/46) of primary SCCOHT samples, but only 4% (15/360) of ovarian clear cell carcinomas; concurrent loss of expression of SMARCA4 and SMARCA2 was found to be highly specific for SCCOHT[349]. Published data investigating the prognostic implications of SMARCA4 alterations in ovarian carcinoma are limited (PubMed, Aug 2022).

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[350]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[351]. Alterations such as seen here may disrupt SMARCA4 function or expression[352-356].

GENE
SOX9

ALTERATION
V306fs*77

HGVS VARIANT
NM_000346.3:c.916del (p.V306Cfs*77)

VARIANT CHROMOSOMAL POSITION
chr17:70119909-70119910

VARIANT ALLELE FREQUENCY (% VAF)
36.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to directly address genomic alterations in SOX9.

FREQUENCY & PROGNOSIS

SOX9 alterations were reported in 1.31% of solid tumors but not in hematologic malignancies[357-361]. Increased expression of SOX9 has been associated with tumor development and/or increased aggressiveness of prostate cancer, pancreatic ductal adenocarcinoma, ovarian cancer, glioma, and esophageal adenocarcinoma[362-365].

FINDING SUMMARY

SOX9 encodes a transcription factor important for the development and differentiation of multiple tissues, including cartilage, testis, and prostate[366].

Dostarlimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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[30-32,45,367] , 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[30-31] . On the basis of prospective clinical data showing efficacy of dostarlimab against various microsatellite instability-high (MSI-H) solid tumors[9,368-370] , MSI-H status may predict sensitivity to dostarlimab.

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab as a single agent, 2 patients with mismatch repair-deficient (dMMR) ovarian cancer were treated, resulting in 1 PR and 1 SD[369]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[9,369,371] . 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[369,372] .

Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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 (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or MMR-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive head and neck squamous cell cancer (HNSCC), cervical cancer, or esophageal cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with non-small cell lung cancer (NSCLC), melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, MSI-H or dMMR endometrial carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma; and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or gastroesophageal junction cancer, renal cell carcinoma, TNBC, urothelial carcinoma, or endometrial carcinoma that is not MSI-H or dMMR. 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[7,373-377], MSI-H status may predict sensitivity to pembrolizumab. On the basis of clinical data across solid tumors[30-32,45,367], 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[30-31].

SUPPORTING DATA

For patients with ovarian cancer enrolled in various clinical trials, a Tumor Mutational Burden (TMB) of 10 Muts/Mb or higher was associated with an ORR of 17% (n=12) on pembrolizumab, whereas a lower TMB was associated with an ORR of 7% (n=281)[378]. The Phase 2 KEYNOTE-158 study of pembrolizumab for patients with advanced previously treated microsatellite instability-high or MMR-deficient non-colorectal cancer reported an ORR of 33% (8/24, 3 CRs), median PFS of 2.2 months, and median OS of 33.6 months for patients with ovarian cancer[379]. The Phase 2 KEYNOTE-100 study of pembrolizumab for patients with platinum-resistant ovarian cancer demonstrated that greater PD-L1 expression (combined positive score [CPS] ≥10) correlated with improved response rate, with ORRs and DCRs of 17% and 42% (7 CRs, 7 PRs, 20 SDs) in the CPS ≥10 cohort, 10% and 38% (7 CRs, 13 PRs, 55 SDs) in the CPS ≥1 cohort, and 5.0% and 33% (7 PRs, 39 SDs) in the CPS <1 cohort, respectively; BRCA mutation status and homologous recombination deficiency status were not associated with ORR[380]. The Phase 1b KEYNOTE-028 study of pembrolizumab in 26 patients with advanced PD-L1-positive (≥1% on tumor or stroma) ovarian cancer reported an ORR of 12% and a DCR of 39% (1 CR, 2 PRs, 7 SDs), with a median PFS and OS of 1.9 and 13.8 months, respectively[381]. Clinical benefit has been observed from the combination of pembrolizumab with niraparib[382] or bevacizumab and cyclophosphamide[383]. In the Phase 2 PEACOCC trial for previously treated ovarian clear cell cancer, treatment with pembrolizumab monotherapy resulted in a PFS rate of 44% at 12 weeks, confirmed DCR of 44% (21/48), and ORR of 25% (12/48; 1 CR, 11 PR); 1-year PFS and OS rates were 22% and 55%, respectively[384].

Atezolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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) as well as adult and pediatric patients 2 years and older with alveolar soft part sarcoma, 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, 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[385] or endometrial cancer[386], MSI-H status may predict sensitivity to atezolizumab. On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] .

SUPPORTING DATA

A case study described a near-complete radiographic response for a patient with PD-L1-negative MSI-H serous ovarian cancer treated with atezolizumab following progression on bevacizumab and chemotherapy[387]. A Phase 1 study of single-agent atezolizumab for patients with advanced or metastatic epithelial ovarian cancer reported an ORR of 22% (2/9), a median PFS (mPFS) of 2.9 months, and a median OS (mOS) of 11.3 months; both objective responses occurred in PD-L1-positive patients (≥5% of immune cells)[388]. A Phase 1b study for patients with platinum-resistant ovarian cancer reported signals of activity and efficacy with the combination of atezolizumab and bevacizumab (ORR of 15% [3/20], DCR of 55% [11/20], mPFS of 4.9 months, and mOS of 10.2 months)[389]. In the placebo-controlled Phase 3 IMagyno50 study, the addition of atezolizumab to bevacizumab and chemotherapy (paclitaxel plus carboplatin) did not improve mPFS for patients with newly diagnosed Stage III or IV ovarian cancer in the intention-to-treat population (19.5 vs. 18.4 months, HR=0.92) or in the PD-L1-positive population (20.8 vs. 18.5 months, HR=0.80)[390]. For patients with relapsed platinum-sensitive ovarian cancer, the Phase 3 ATALANTE trial reported the addition of atezolizumab to bevacizumab plus platinum-based chemotherapy did not improve mPFS in the intent-to-treat population (13.5 vs. 11.3 months, HR=0.83) or the PD-L1 positive population (15.2 vs. 13.1 months, HR=0.86), though mOS was numerically longer in the atezolizumab cohort (35.5 vs. 30.6 months, HR=0.81)[391]. In a Phase 2b study for patients with recurrent platinum-resistant ovarian, Fallopian tube, or primary peritoneal cancer, the addition of acetylsalicylic acid to atezolizumab and bevacizumab did not significantly improve outcomes relative to the addition of placebo[392]. In the prospective Phase 2a MyPathway basket study evaluating atezolizumab for patients with TMB-High solid tumors, patients with TMB ≥16 Muts/Mb achieved improved ORR (38% [16/42] vs. 2.1% [1/48]), DCR (62% [26/42] vs. 23% [11/48]), mPFS (5.7 vs. 1.8 months, HR 0.34), and mOS (19.8 vs. 11.4, HR 0.53) as compared to those with TMB ≥10 and <16 Muts/Mb[42]. 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%)[45].

Avelumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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[385], endometrial cancer[386], or gastric/gastroesophageal junction cancer[393], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab. On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] .

SUPPORTING DATA

A Phase 1b study of single-agent avelumab reported that patients with recurrent or refractory ovarian, fallopian tube, or peritoneal cancer achieved an ORR of 9.6% (12/125), a DCR of 52% (65/125), a median PFS (mPFS) of 2.6 months, and a median OS of 11.2 months; response did not correlate with tumor PD-L1 expression status[394]. In the JAVELIN Ovarian 200 Phase 3 study, the addition of avelumab to pegylated liposomal doxorubicin (PLD) did not improve mPFS (3.7 vs. 3.5 months, HR=0.78) or OS (15.7 vs. 13.1 months, HR=0.89) for unselected patients with platinum-resistant or refractory ovarian, fallopian tube, or peritoneal cancer compared with PLD alone[395]. In the Phase 3 JAVELIN Ovarian 100 study, avelumab plus chemotherapy regimens did not improve mPFS (16.8-18.1 months vs. not estimable, HR=1.43 and 1.14) compared with chemotherapy alone for patients with treatment-naive ovarian, fallopian tube, or peritoneal cancer[396].

Cemiplimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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 non-small cell lung cancer (NSCLC), cutaneous squamous cell carcinoma, or basal cell carcinoma. 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[3,6-7,373-376] , MSI-H status may predict sensitivity to cemiplimab. On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] .

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of ovarian cancer are limited (PubMed, Feb 2023). Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[397]. A Phase 2 trial of cemiplimab in patients with basal cell carcinoma (BCC) reported ORRs of 31% (5 CRs and 21 PRs) in patients with locally advanced BCC and 21% (6 PRs) in patients with metastatic BCC[398-399] . 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[400].

Durvalumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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), small cell lung cancer (SCLC), and biliary tract cancer. 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[385], endometrial cancer[386], or gastric/gastroesophageal junction cancer[393], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab. On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] .

SUPPORTING DATA

Durvalumab has been primarily studied in combination with other agents in ovarian cancers. In a Phase 2 study of durvalumab and olaparib, patients with ovarian cancer achieved an ORR of 15% and a DCR of 53% (5 PR, 13 SD in 34 patients); responses were seen in both BRCA-mutated and BRCA-wildtype patients[401]. A study of durvalumab in combination with chemotherapy in patients with newly diagnosed ovarian cancer reported an ORR of 67% (12/18; 1 CR, 11 PRs) and median PFS of 14.5 months[402]. A study comparing durvalumab to physician's choice chemotherapy for patients with recurrent ovarian clear cell carcinoma reported no significant differences in ORR (11% vs. 19%) or median PFS (7.4 vs 14.0 weeks) following treatment with durvalumab compared to chemotherapy[403]. In a Phase 1 study of durvalumab in combination with olaparib and cediranib, patients with ovarian cancer achieved an ORR of 29% (2/7)[404].

Durvalumab + Tremelimumab

Assay findings association

Microsatellite status
MSI-High

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; tremelimumab is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibody. These therapies are FDA approved in combination to treat adult patients with unresectable hepatocellular carcinoma and metastatic non-small cell lung cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[10-11,405-406] , microsatellite instability high (MSI-H) status may predict sensitivity to combination durvalumab and tremelimumab.

SUPPORTING DATA

A Phase 2 umbrella study of patients with platinum-resistant ovarian cancer reported 1 CR and 10 PRs across 2 cohorts for the combination treatment with durvalumab and tremelimumab plus chemotherapy, with 2 different doses of tremelimumab[407]. Another Phase 2 study of durvalumab and tremelimumab added to frontline neoadjuvant chemotherapy for patients with advanced epithelial ovarian cancer reported an overall ORR of 87%[408].

Nivolumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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 as a monotherapy 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, colorectal cancer (CRC), classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma or squamous cell carcinoma (ESCC). It is also approved in combination with chemotherapy to treat ESCC, in combination with cabozantinib to treat RCC, and in combination with relatlimab to treat melanoma. 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[3,6] , MSI-H status may predict sensitivity to nivolumab. On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] .

SUPPORTING DATA

A Phase 2 study of nivolumab for patients with platinum-resistant ovarian cancer reported an ORR of 15% (3/20), a DCR of 45% (9/20), a median PFS of 3.5 months, and a median OS of 20.0 months (at study termination); 10% (2/20) of patients experienced durable CRs[409]. Similar nivolumab efficacy was seen in a retrospective study in a similar setting[410]. In another Phase 2 study, patients with recurrent or persistent ovarian cancer treated with nivolumab combined with ipilimumab experienced significantly improved ORR (31% [16/51] vs. 12% [6/49]) and median PFS (3.9 vs. 2 months; HR=0.53) than those treated with nivolumab alone; median OS was numerically higher in the combinational group (28.1 vs. 21.8 months), although this result did not reach statistical significance[411]. A Phase 2 study combining nivolumab and bevacizumab for patients with relapsed ovarian cancer reported median PFS rates of 12.1 and 7.7 months and ORRs of 40% (8/20) and 17% (3/18) for patients with platinum-sensitive and platinum-resistant cancer, respectively[412]. A Phase 1 trial of nivolumab included 17 cases with ovarian cancer and observed disease control for 24% (1 PR, 3 SDs) of these patients[413]. A retrospective case series of 6 patients who were treated with nivolumab as salvage therapy for germline BRCA1/2-mutated recurrent epithelial ovarian and Fallopian tube cancers reported an ORR of 67%, with 3 CRs, 1 PR, and 2 PDs[414].

Nivolumab + Ipilimumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 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), pleural mesothelioma, and esophageal squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[33-34,415] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment. On the basis of clinical data across solid tumors[3-5,416-420] , microsatellite instability high (MSI-H) status may predict sensitivity to combination nivolumab and ipilimumab.

SUPPORTING DATA

In a Phase 2 study, patients with recurrent or persistent ovarian cancer treated with nivolumab combined with ipilimumab experienced significantly improved ORR (31% [16/51] vs. 12% [6/49]) and median PFS (3.9 vs. 2.0 months; HR=0.53) than those treated with nivolumab alone; median OS was numerically higher in the combinational group (28.1 vs. 21.8 months), although this result did not reach statistical significance[411].

Retifanlimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Retifanlimab 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 Merkel cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[30-32,45,367] , 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[30-31] . On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[3,6-7,373-376,421] , MSI-H status may predict sensitivity to retifanlimab.

SUPPORTING DATA

Clinical data on the efficacy of retifanlimab for the treatment of ovarian cancer are limited (PubMed, Apr 2023). The efficacy of retifanlimab has been demonstrated in various treatment settings for multiple advanced solid tumors, including Merkel cell carcinoma[422], anal squamous cell carcinoma (SCC)[423], microsatellite instability-high or deficient MMR endometrial carcinoma[421], glioblastoma[424], soft tissue sarcoma[425], and gastroesophageal adenocarcinoma[426]. The Phase 2 POD1UM-201 trial of retifanlimab for patients with chemotherapy-naive advanced Merkel cell carcinoma reported an ORR of 51% (33/65; 11 CRs, 22 PRs), unreached median duration of response, and median PFS (mPFS) of 13.8 months[422]. In the Phase 2 POD1UM-202 study for patients with previously treated advanced squamous carcinoma of the anal canal, retifanlimab elicited an ORR of 14% (13/94; 1 CR, 12 PRs), mPFS of 2.3 months, and median OS of 10.1 months, with responses observed regardless of PD-L1 expression[423]. In the Phase 2 POD1UM-203 trial for multiple tumor types, retifanlimab yielded an ORR of 35% (8/23) and mPFS of 4.4 months for patients with treatment-naive metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (TPS ≥50%), an ORR of 40% (14/35) and mPFS of 3.6 months for patients with unresectable or metastatic melanoma, an ORR of 38% (11/29) and mPFS of 5.7 months for patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma with PD-L1 expression (CPS ≥10%), and an ORR of 24% (8/34; 1 CR, 7 PRs) and mPFS of 5.4 months for patients with treatment-naive advanced clear cell renal cell carcinoma (RCC)[427].

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.

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

RESULT

MSI-High

RATIONALE

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

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT02628067

PHASE 2

Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/ KEYNOTE-158)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Makati (Philippines), Seoul (Korea, Republic of), North Ryde (Australia), Moscow (Russian Federation), Hod Hasharon (Israel), Drammen (Norway), Glostrup (Denmark), Haar (Germany), Haarlem (Netherlands)

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS
HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT04152018

PHASE 1

Study of PF-06940434 in Patients With Advanced or Metastatic Solid Tumors.

TARGETS
PD-1, Integrin alpha-V

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Liverpool (Australia), Wollongong (Australia), Bratislava (Slovakia), Washington, California, Arizona, New York

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy), Meldola (Italy)

NCT05092360

PHASE 3

Phase 3 Study of Nemvaleukin Alfa in Combination With Pembrolizumab

TARGETS
IL-2R, PD-1

LOCATIONS: Chang Hua (Taiwan), Taichung (Taiwan), Taipei (Taiwan), Daegu (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Singapore (Singapore), South Brisbane (Australia), Adelaide (Australia), East Melbourne (Australia)

NCT04215978

PHASE 1

Safety and Preliminary Effectiveness of BGB-A445 in Combination With Tislelizumab in Participants With Advanced Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: Changhua (Taiwan), Taipei (Taiwan), Tianan (Taiwan), Hangzhou (China), Shanghai (China), Changsha (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Gyeongju (Korea, Republic of)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

NCT04282018

PHASE 1/2

Brief Title: Study of BGB-10188 as Monotherapy, and in Combination With Zanubrutinib, and Tislelizumab

TARGETS
PI3K-delta, PD-1, BTK

LOCATIONS: Fuzhou (China), Zhejiang (China), Shanghai (China), Suzhou (China), Changsha (China), Jining (China), Chengdu (China), West Perth (Australia), Adelaide (Australia), Blacktown (Australia)

BIOMARKER

Tumor Mutational Burden

RESULT

14 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.

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT04589845

PHASE 2

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China)

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS
HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT04152018

PHASE 1

Study of PF-06940434 in Patients With Advanced or Metastatic Solid Tumors.

TARGETS
PD-1, Integrin alpha-V

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Liverpool (Australia), Wollongong (Australia), Bratislava (Slovakia), Washington, California, Arizona, New York

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy), Meldola (Italy)

NCT05092360

PHASE 3

Phase 3 Study of Nemvaleukin Alfa in Combination With Pembrolizumab

TARGETS
IL-2R, PD-1

LOCATIONS: Chang Hua (Taiwan), Taichung (Taiwan), Taipei (Taiwan), Daegu (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Singapore (Singapore), South Brisbane (Australia), Adelaide (Australia), East Melbourne (Australia)

NCT04215978

PHASE 1

Safety and Preliminary Effectiveness of BGB-A445 in Combination With Tislelizumab in Participants With Advanced Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: Changhua (Taiwan), Taipei (Taiwan), Tianan (Taiwan), Hangzhou (China), Shanghai (China), Changsha (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Gyeongju (Korea, Republic of)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

NCT04282018

PHASE 1/2

Brief Title: Study of BGB-10188 as Monotherapy, and in Combination With Zanubrutinib, and Tislelizumab

TARGETS
PI3K-delta, PD-1, BTK

LOCATIONS: Fuzhou (China), Zhejiang (China), Shanghai (China), Suzhou (China), Changsha (China), Jining (China), Chengdu (China), West Perth (Australia), Adelaide (Australia), Blacktown (Australia)

GENE
ARID1A

ALTERATION
G324fs*39

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors. On the basis of preclinical evidence, ARID1A loss or inactivation may predict sensitivity to EZH2 and BET/BRD inhibitors.

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Girona (Spain), Badalona (Spain), Barcelona (Spain), Zaragoza (Spain), Valencia (Spain), Madrid (Spain), El Palmar (Spain), A Coruña (Spain), Córdoba (Spain)

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Montana, California, Colorado, Arizona, Michigan, Texas

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Colorado, Illinois, Texas, North Carolina, Georgia

NCT04802174

PHASE 1/2

Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT04104776

PHASE 1/2

A Study of CPI-0209 in Patients With Advanced Solid Tumors

TARGETS
EZH2, TOP1

LOCATIONS: Washington, Salamanca (Spain), Michigan, Illinois, Ohio, Massachusetts, New Jersey, New York

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
TOP1, ATR

LOCATIONS: California, Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, New York

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT04840589

PHASE 1

Testing the Combination of ZEN003694 and Nivolumab With or Without Ipilimumab in Solid Tumors

TARGETS
PD-1, CTLA-4, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Ohio, Pennsylvania, New York, Maryland

NCT05071937

PHASE 2

ZEN003694 Combined With Talazoparib in Patients With Recurrent Ovarian Cancer

TARGETS
BRD4, BRDT, BRD2, BRD3, PARP

LOCATIONS: Pennsylvania

GENE
ATM

ALTERATION
S214fs*40

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT05489211

PHASE 2

Study of Dato-Dxd as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Tumours (TROPION-PanTumor03)

TARGETS
TROP2, PD-L1, PARP1, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Liou Ying Township (Taiwan), Shanghai (China), Seoul (Korea, Republic of), Seodaemun-gu (Korea, Republic of), Suita-shi (Japan), Chuo-ku (Japan), Koto-ku (Japan), Kashiwa (Japan)

NCT04434482

PHASE 1

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Gyeonggi-do (Korea, Republic of), Orange (Australia), Blacktown (Australia), Albury (Australia)

NCT04884360

PHASE 3

D9319C00001- 1L OC Mono Global RCT

TARGETS
PARP

LOCATIONS: Rui'an (China), Wenzhou (China), Jiaxing (China), Shanghai (China), Suzhou (China), Wuxi (China), Nanjing (China), Hefei (China), Guangzhou (China), Urumqi (China)

NCT04518501

PHASE 1/2

Fuzuloparib Arsenic Trioxide Platinum Resistance Relapsed Ovarian Cancer

TARGETS
RARA, PARP

LOCATIONS: Zhejiang (China)

NCT04517357

PHASE 2

A Phase 2 Trial of Fluzoparib Combined With Apatinib Versus Fluzoparib Monotherapy in Treatment With Relapsed Ovarian Cancer Patients

TARGETS
RET, SRC, VEGFR2, KIT, PARP

LOCATIONS: Hangzhou (China)

NCT05489926

PHASE 2

A Study to Explore Pamiparib Treatment in Epithelial Ovarian Cancer After Prior PARP Inhibitor Exposure

TARGETS
PARP

LOCATIONS: Hangzhou (China)

NCT03983226

PHASE 2

Surgery and Niraparib in Secondary Recurrent Ovarian Cancer (SOC-3 Trial)

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT05652283

PHASE 2

Pamiparib Combined With Surufatinib for the Neoadjuvant Treatment of Unresectable Ovarian Cancer

TARGETS
FGFR1, CSF1R, VEGFRs, PARP

LOCATIONS: Hefei (China)

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: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

GENE
PIK3R1

ALTERATION
Y452_N453>H, W597fs*2, E601fs*57

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors.

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT05082025

PHASE 2

Phase 2 Study of PI3K Inhibitor Copanlisib in Combination With Fulvestrant in Selected ER+ and/or PR+ Cancers With PI3K (PIK3CA, PIK3R1) and/or PTEN Alterations

TARGETS
ER, PI3K

LOCATIONS: Texas

NCT04975958

PHASE 1

Double/Triple Combinations of AN2025, AN0025 and Atezolizumab in Advanced Solid Tumors

TARGETS
PI3K, PD-L1, EP4

LOCATIONS: Colorado, Oklahoma, New York, New Jersey, Florida

NCT03586661

PHASE 1

Niraparib and Copanlisib in Treating Participants With Recurrent Endometrial, Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

TARGETS
PI3K, PARP

LOCATIONS: Texas

GENE
PTEN

ALTERATION
R130P, T319fs*1

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04434482
PHASE 1

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Gyeonggi-do (Korea, Republic of), Orange (Australia), Blacktown (Australia), Albury (Australia)

NCT04884360
PHASE 3

D9319C00001- 1L OC Mono Global RCT

TARGETS
PARP

LOCATIONS: Rui'an (China), Wenzhou (China), Jiaxing (China), Shanghai (China), Suzhou (China), Wuxi (China), Nanjing (China), Hefei (China), Guangzhou (China), Urumqi (China)

NCT04518501
PHASE 1/2

Fuzuloparib Arsenic Trioxide Platinum Resistance Relapsed Ovarian Cancer

TARGETS
RARA, PARP

LOCATIONS: Zhejiang (China)

NCT04517357
PHASE 2

A Phase 2 Trial of Fluzoparib Combined With Apatinib Versus Fluzoparib Monotherapy in Treatment With Relapsed Ovarian Cancer Patients

TARGETS
RET, SRC, VEGFR2, KIT, PARP

LOCATIONS: Hangzhou (China)

NCT05489926
PHASE 2

A Study to Explore Pamiparib Treatment in Epithelial Ovarian Cancer After Prior PARP Inhibitor Exposure

TARGETS
PARP

LOCATIONS: Hangzhou (China)

NCT03983226
PHASE 2

Surgery and Niraparib in Secondary Recurrent Ovarian Cancer (SOC-3 Trial)

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT05652283

PHASE 2

Pamiparib Combined With Surufatinib for the Neoadjuvant Treatment of Unresectable Ovarian Cancer

TARGETS
FGFR1, CSF1R, VEGFRs, PARP

LOCATIONS: Hefei (China)

NCT04931342

PHASE 2

A Study Evaluating the Efficacy and Safety of Biomarker-Driven Therapies in Patients With Persistent or Recurrent Rare Epithelial Ovarian Tumors

TARGETS
AKTs, MEK, ERBB2, PD-L1, VEGFA

LOCATIONS: Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Moskva (Russian Federation), Malvern (Australia), Ankara (Turkey), Istanbul (Turkey), Brno (Czechia), Dresden (Germany), Prague (Czechia), Muenchen (Germany)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT05170594

PHASE 2

A Study of Bevacizumab Combined With Fluzoparib/Chemotherapy or Fluzoparib in the Treatment of Ovarian Cancer

TARGETS
PARP, VEGFA

LOCATIONS: Tai'an (China)

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.

ARAF
NM_001654.3: c.1112G>T
(p.G371V)
chrX:47428152

CTCF
NM_006565.3: c.781G>T
(p.G261C)
chr16:67645516

DIS3
NM_001128226.1: c.1481C>T
(p.A494V)
chr13:73345967

EGFR
NM_005228.3: c.1913C>T
(p.T638M)
chr7:55238900

EPHA3
NM_005233.4: c.1751G>T
(p.G584V)
chr3:89457270

FH
NM_000143.3: c.124G>A
(p.A42T)
chr1:241682899

FLCN
NM_144997.5: c.992C>T
(p.S331F)
chr17:17122403

GATA3
NM_001002295.1: c.221G>T
(p.R74M)
chr10:8097839

GID4 (C17ORF39)
NM_024052.4: c.224C>G
(p.P75R)
chr17:17943002

GNAQ
NM_002072.3: c.161C>T
(p.T54M)
chr9:80537237

IGF1R
NM_000875.3: c.3982G>A
(p.G1328S)
chr15:99500549

IKBKE
NM_014002.3: c.1367G>A
(p.R456Q)
chr1:206653816

NOTCH3
NM_000435.2: c.4793A>T
(p.D1598V)
chr19:15281580

NTRK1
NM_002529.3: c.1052C>A
(p.P351H)
chr1:156843626

POLE
NM_006231.2: c.5270G>A
(p.S1757N)
chr12:133218341

RAD51D
NM_001142571.1: c.155C>T
(p.A52V)
chr17:33444046

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 or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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

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

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 PRINCIPLE

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 Therapies and Clinical Trials

Ranking of Therapies in Summary Table
Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of 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. 2023. 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. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

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 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. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. 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.
6. 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.
7. 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%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

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 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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.9.0

The median exon coverage for this sample is 866x

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