FOUNDATIONONE®CDx

PATIENT
Li, Meng-Ju

TUMOR TYPE
Uterus endometrial adenocarcinoma endometrioid

COUNTRY CODE
TW

REPORT DATE
28 Sep 2021

ORDERED TEST #
ORD-1194331-01

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 Uterus endometrial adenocarcinoma endometrioid
NAME Li, Meng-Ju
DATE OF BIRTH 12 December 1974
SEX Female
MEDICAL RECORD # 47551224

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Uterus
SPECIMEN ID S110-67168 R (PF21018)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 18 August 2021
SPECIMEN RECEIVED 21 September 2021

Biomarker Findings

Tumor Mutational Burden - 372 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

FBXW7 R441W
PIK3CA R88Q, T1025A
ATM R250*
BRCA2 E1879D
NF1 R1362*, R2450*
CTNNB1 K335T
FANCL splice site 904-2A>C
FGFR2 N549D
PIK3CB R321Q
PIK3R1 E476*
PTEN R130Q, R173H
RAD51D R253Q
TSC1 Q739*
APC S2307L, R2204*
ATRX R907*
CARD11 R271W
CREBBP E50*
CTCF R129*
CTNNA1 R451*
CUL3 L602*
ESR1 R256Q
FAM123B E387*
KEL E494*
KLHL6 D104N
MAP3K1 G914*
MLL2 R5214C
MSH6 E641*
POLE V411L
SETD2 splice site 5278-1G>T
SPEN A2727V
STAG2 splice site 463-1G>T
TNFAIP3 R87*
TP53 F113V - subclonal, T211A†
XPO1 R749Q
ZNF217 D326N

† See About the Test in appendix for details.

16 Therapies with Clinical Benefit
0 Therapies with Resistance
56 Clinical Trials

PATHOLOGIST COMMENTS

Douglas Lin, M.D. 28-Sep-2021

The genomic profile is compatible with a POLE-ultramutated endometrial carcinoma.

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 372 Muts/Mb	Dostarlimab 2A	Avelumab 2A
	Pembrolizumab 2A	Nivolumab 2A
		Atezolizumab
		Cemiplimab
		Durvalumab
		Nivolumab + Ipilimumab
10 Trials *see p. 37*		
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FBXW7 - R441W	none	Everolimus 2A
		Temsirolimus 2A
10 Trials *see p. 47*		
PIK3CA - R88Q, T1025A	none	Everolimus 2A
		Temsirolimus 2A
10 Trials *see p. 53*		
ATM - R250*	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials *see p. 39*		
BRCA2 - E1879D	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials *see p. 41*		
NF1 - R1362*, R2450*	none	Selumetinib
		Trametinib
10 Trials *see p. 51*		
CTNNB1 - K335T	none	none
9 Trials *see p. 43*		
FANCL - splice site 904-2A>C	none	none
10 Trials *see p. 45*		
FGFR2 - N549D	none	none
9 Trials *see p. 49*		
PIK3CB - R321Q	none	none
10 Trials *see p. 55*		
PIK3R1 - E476*	none	none
4 Trials *see p. 57*		
PTEN - R130Q, R173H	none	none
10 Trials *see p. 58*		
RAD51D - R253Q	none	none
10 Trials *see p. 60*		

NCCN category

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
TSC1 **-** Q739*	none	none
10 Trials *see p. 62*		

☐ *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 **-** R250* p. 5 ***MSH6*** **-** E641* p. 20

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

MLL2 **-** R5214C p. 19

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.

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BIOMARKER

Tumor Mutational Burden

RESULT
372 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[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[1-4,11]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[1]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[12] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[2]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[4,11]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that endometrial adenocarcinomas harbored a median TMB of 4.5 Muts/Mb, and 15% of cases had an elevated TMB of greater than 20 Muts/Mb[13]. Another study evaluating TMB in endometrial adenocarcinoma reported that 24% of tumors had a mutational burden of greater than 10.4 Muts/Mb[14]. Increased tumor mutational burden (TMB) in endometrial carcinoma has been correlated with POLE mutation and advanced high-grade endometrioid subtypes[15-18]. Ultramutated endometrial tumors (elevated TMB with POLE mutations) have also been associated with improved PFS[16]. The same study associated lower mutational burden, independent of PD-L1 status, in endometrial carcinomas with poorer prognosis[16]. For patients with advanced microsatellite-stable endometrial carcinoma not treated with immunotherapy, OS did not significantly differ between patients with TMB-high (≥10 Muts/Mb) and TMB-low (11.4 vs. 13.5 months, adjusted HR=1.15) in 1 study[19].

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[20-21] and cigarette smoke in lung cancer[22-23], treatment with temozolomide-based chemotherapy in glioma[24-25], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16,26-29], and microsatellite instability (MSI)[16,28-29]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[2-4,11].

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[30-32], including approved therapies nivolumab and pembrolizumab[33]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[34].

FREQUENCY & PROGNOSIS

MSS has been reported in 73-89% of endometrial cancers[16,18,35-40]. Data regarding the role of MSI status on prognosis and survival in endometrial cancer are conflicting, with most studies finding no relationship between MSI-H endometrial cancers and survival[36-37,39,41-43], and one study predicting improved disease-free and disease-specific survival[35]. However, these studies often evaluated endometrial cancers of all FIGO stages together. Studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[36,40,44-45], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

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[46]. 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[46-48]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[49-51]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[46,48,50-51].

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GENE
ATM

ALTERATION
R250*

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
748C>T

VARIANT ALLELE FREQUENCY (% VAF)
34.1%

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[52]. Clinical data in prostate cancer[53-55], gastric cancer[56], colorectal cancer[57], breast cancer[57], papillary renal cell carcinoma[58], and cholangiocarcinoma[59] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[60-67]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[68] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[69] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[70-72] and hematologic malignancies[70,73] 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[74].

FREQUENCY & PROGNOSIS

ATM mutation and homozygous deletion have been observed in 11-12% and up to 1.8% (5/761) samples of endometrial carcinoma, respectively (cBioPortal, COSMIC, Mar 2021)[75-77]. Altered expression of ATM has been reported in 4.5% (1/22) of endometrial hyperplasia samples and in 3.3% (2/61) of endometrioid-type endometrial cancer samples analyzed in one study[78]. Hypermethylation of ATM has been reported in 11% of endometrial carcinomas[79]. Conflicting findings have been reported regarding the prognostic implications of ATM expression in endometrial carcinomas, with one study reporting a negative correlation between ATM expression and pathological grade[80] and another a positive correlation between increased ATM expression and unfavorable clinicopathologic features, including increased tumor grade and reduced 5-year recurrence free survival[81].

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[82]. Loss of functional ATM promotes tumorigenesis[83]. Alterations such as seen here may disrupt ATM function or expression[84-86].

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, Mar 2021)[87]. 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 female carriers displaying a 38% lifetime risk of breast cancer[88]. 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[89]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[82,89]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[89]. 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[90-95]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[94,96-97]. 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
BRCA2

ALTERATION
E1879D

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
5637G>T

VARIANT ALLELE FREQUENCY (% VAF)
10.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[53,98-114] or ATR inhibitors[69,115-116]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[53,103,106,113-114] and for patients with platinum-resistant or -refractory disease[98,102,109,112]. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib[116]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[117], ovarian carcinoma[118], and triple-negative breast cancer (TNBC)[119] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[120]. In a Phase 1 monotherapy trial of adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[121]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— Nontargeted Approaches —

Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[122-132].

FREQUENCY & PROGNOSIS

BRCA2 mutation has been reported in 10% of uterine corpus endometrial and endometrioid carcinoma cases analyzed in the TCGA dataset[16]. LOH of the wild type BRCA1/2 allele in patients with endometrial carcinoma harboring germline BRCA1/2 mutations has been associated with higher FIGO grade, nonendometrioid histology, and frequent co-occurrence of TP53 mutation[133]. Studies have reported that BRCA2 germline mutations do not increase the lifetime risk of endometrial cancer[134-135].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[136]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[137]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[138-139], and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively[140]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[141]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[140,142-147]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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GENE
FBXW7

ALTERATION
R441W

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
1321C>T

VARIANT ALLELE FREQUENCY (% VAF)
34.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[148-149]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[150], renal cell carcinoma[58], and cervical squamous cell carcinoma[151]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— Nontargeted Approaches —

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[152].

FREQUENCY & PROGNOSIS

FBXW7 mutations have been reported in 14.2% of endometrial carcinomas (COSMIC, Feb 2021)[77]. Studies have variously reported FBXW7 mutation in 18-29% of uterine serous carcinoma, 16% of endometrial cancer, and 2% of endometrioid endometrial cancer cases[153-157]. In primary endometrial carcinomas, FBXW7 mutations correlated with lymph node involvement[158].

Reduced FBXW7 expression has been associated with poor prognosis in some cancers such as colorectal cancer, gastric cancer, esophageal SCC, cervical SCC, melanoma, and non-small cell lung carcinoma[159-166].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[167]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[167-168]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
NF1

ALTERATION
R1362*, R2450*

TRANSCRIPT ID
NM_001042492, NM_001042492

CODING SEQUENCE EFFECT
4084C>T, 7348C>T

VARIANT ALLELE FREQUENCY (% VAF)
34.5%, 71.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[169-172], glioma or glioblastoma[172-176], non-small cell lung cancer[177], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[178-180] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[181-182]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[183]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[184], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[185].

FREQUENCY & PROGNOSIS

NF1 alterations have been reported in 5-9% of endometrial carcinomas[16,186-187]. Loss of NF1 has been reported in 13% (4/31) of endometrial carcinomas[188]. Published data investigating the prognostic implications of NF1 mutation in endometrial carcinomas are limited (PubMed, Feb 2021).

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[189]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[190]. Alterations such as seen here may disrupt NF1 function or expression[190-199].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the NF1 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 neurofibromatosis type 1 (ClinVar, Mar 2021)[87]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[200-202]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[203-204], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
PIK3CA

ALTERATION
R88Q, T1025A

TRANSCRIPT ID
NM_006218, NM_006218

CODING SEQUENCE EFFECT
263G>A, 3073A>G

VARIANT ALLELE FREQUENCY (% VAF)
36.3%, 37.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[205-207], AKT[208-209], or mTOR[178,210-216]. Results from the Phase 2 MATCH trial for patients with PIK3CA-altered solid tumors found that 27% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[217]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[218]. The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study of PIK3CA-mutated solid tumors[219]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-altered tumors[220-221].

— Potential Resistance —

Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[222-226].

FREQUENCY & PROGNOSIS

In the scientific literature, PIK3CA mutations have been reported in 16-54% of endometrial carcinomas[16,158,227]. In endometrial cancers, PIK3CA mutations often co-occur with other mutations that activate the PI3K-AKT-mTOR signaling axis, such as PTEN and KRAS alterations[228-229]. Overexpression of p110-alpha has been reported in 72% of endometrial carcinomas[230]. One study reported PIK3CA exon 9 or 20 mutations in 20% (20/99) of high-grade endometrial carcinomas; these mutations were associated with shorter patient survival within Grade 3 endometrioid carcinoma, but not within endometrial serous carcinoma[231].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[232-233]. PIK3CA alterations that have been characterized as activating, such as R88Q observed here, are predicted to be oncogenic[227,229,234-252]. Although alterations such as T1025A seen here have not been fully characterized, they have been associated with sensitivity to targeted therapies or have shown cancer association, which may indicate biological relevance[75-77,246,253-255].

GENE
CTNNB1

ALTERATION
K335T

TRANSCRIPT ID
NM_001904

CODING SEQUENCE EFFECT
1004A>C

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[256-258]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[180,259] or endometrial carcinoma[254]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[260-262]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate in 2 out of 4 patients and SD rate of in 1 out of 4 patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[263]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[264-267]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[268-269], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[257,270-272]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

CTNNB1 mutations have been reported in 7-45% of endometrial carcinomas (ECs)[16,273-276]. CTNNB1 mutations are more common in Type 1 EC than Type 2[277-278]. In addition, one study found that CTNNB1 mutations were identified more frequently in sporadic ECs (31%, 18/58), than in Lynch syndrome (LS)-associated ECs (6.9%, 2/29)[276]. Nuclear beta-catenin protein expression has been observed in 14.7-27.6% (33/224-55/199) of ECs, with a significantly higher incidence in Type 1 tumors[274,279]. Multiple studies have reported that CTNNB1 mutation characterizes an aggressive subset of EC[44,280-281]. One study found that that TP53 or CTNNB1 mutation was an independent marker of poor recurrence-free survival (HR=4.69) for patients with low grade, early stage EC[280]. Low membrane expression of beta-catenin has been linked with poor prognosis in EC and ovarian endometrioid carcinomas[282-283].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[284]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
FANCL

ALTERATION
splice site 904-2A>C

TRANSCRIPT ID
NM_018062

CODING SEQUENCE EFFECT
904-2A>C

VARIANT ALLELE FREQUENCY (% VAF)
32.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FANCL. Clinical evidence in ovarian cancer indicates that FANCL inactivation may confer sensitivity to PARP inhibitors[285-286] .

FREQUENCY & PROGNOSIS

FANCL mutations are most frequently observed in tumors of the prostate (5.9%), liver (4.1%), biliary tract (3.4%), endometrium (3.2%), pancreas (2.7%), large intestine (2.4%), and stomach (2.4%) (COSMIC, May 2021)[77]. Published data investigating the prognostic implications of FANCL alterations in solid tumors and hematologic malignancies are limited (PubMed, May 2021). In a prospective study of 255 patients with follicular lymphoma, 2p gain, which includes VRK2, FANCL, and LINC01122, was associated with worse PFS and OS in multivariate analysis[287].

FINDING SUMMARY

FANCL encodes a member of the Fanconi anemia nuclear complex, a multiprotein structure also including the products of FANCA, FANCC, FANCF and FANCG. The activity of this complex is essential to prevention of chromosome breakage caused by DNA damage[288]. Germline mutations in FANCL cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair[289]. Alterations such as seen here may disrupt FANCL function or expression[290-297]. Germline mutations in FANCL, such as T367fs*13, have been associated with Fanconi anemia, breast cancer, and ovarian cancer and with an increased risk of esophageal cancer and prostate cancer[298-302].

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GENE
FGFR2

ALTERATION
N549D

TRANSCRIPT ID
NM_000141

CODING SEQUENCE EFFECT
1645A>G

VARIANT ALLELE FREQUENCY (% VAF)
34.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGFR2 activating mutations, amplifications, or fusions may confer sensitivity to selective FGFR inhibitors such as erdafitinib[303], pemigatinib[304-305], infigratinib[306], E7090[307], AZD4547[308-310], Debio 1347[311-312], rogaratinib[313], futibatinib[314], and derazantinib[315] as well as to the multikinase inhibitors pazopanib[316-317] and ponatinib[318]. Cases of clinical response to selective FGFR inhibitors have been reported for patients with various FGFR2-mutated tumors, including PRs for patients with FGFR2-mutated cholangiocarcinoma treated with AZD4547[319] or erdafitinib[320] and a PR for a patient with FGFR2-mutated lung squamous cell carcinoma treated with infigratinib[321]. A patient with endometrioid adenocarcinoma and cervical cancer and both an FGFR2 amplification and mutation experienced a PR following treatment with Debio-1347[311]. Additional clinical responses associated with FGFR2 mutation have been reported for a patient with HNSCC[317], and in a patient with solitary fibrous tumor treated with pazopanib[322].

FREQUENCY & PROGNOSIS

FGFR2 mutations have been reported in 12.5% of cases in the Uterine Corpus Endometrioid Carcinoma TCGA dataset[16]. In the scientific literature, mutation of FGFR2 has been identified in 10.3% (48/466) of endometrial carcinoma (EC) tumors in one study, and at similar frequencies in others[323-325]. FGFR2 expression has been identified in 71.9% (23/32) of EC specimens in one study; however, levels of FGFR2 protein or FGFR2 mRNA have not been consistently demonstrated to be higher in tumor specimens compared to normal endometrial tissues[326-328]. FGFR2 mutations in endometrioid endometrial tumors have been correlated with decreased disease-free survival in one study[325].

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[329-330]. FGFR2 mutations that have been characterized as activating, such as observed here, are predicted to be oncogenic[324-325,331-341]. FGFR2 activating alterations that affect amino acid E565 and mutations such as S252W, P253R, W290C, S372C, Y375C, N549K, and K659E have been reported in patients with Apert, Pfeiffer, Beare-Stevenson, and Crouzon syndromes and syndromic craniosynostosis[324,341-349].

GENE
PIK3CB

ALTERATION
R321Q

TRANSCRIPT ID
NM_006219

CODING SEQUENCE EFFECT
962G>A

VARIANT ALLELE FREQUENCY (% VAF)
36.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence indicates that PTEN-deficient tumors depend on PI3K-beta[350-352], and inhibitors selective for PI3K-beta, including GSK2636771 and AZD8186, are in clinical trials for PTEN-deficient tumors[353-354] . PIK3CB activating alterations may further refine the use of PI3K-beta-selective inhibitors[355]. Two patients with PTEN-deficient prostate tumors and concurrent PIK3CB L1049R mutation or PIK3CB amplification derived significant clinical benefit from treatment with GSK2636771[356]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrial Carcinoma TCGA dataset, PIK3CB mutations and amplification have been observed in 5.4% and 2.1% of cases, respectively[16]. Published data investigating the prognostic implications of PIK3CB alterations in endometrial carcinoma are limited (PubMed, Oct 2020). However, a preclinical study reported that elevated PIK3CB mRNA levels contributed to early endometrial tumorigenesis and increased cellular proliferation of primary tumors[357].

FINDING SUMMARY

PIK3CB (PI3K-beta, p110-beta) encodes a member of the class IA phosphoinositide 3-kinases (PIK3CA, PIK3CB, PIK3CD, and PIK3CG), which are essential regulators of cellular proliferation, survival, metabolism, and motility. Dysregulation of the PI3K signaling pathway is observed in many human cancers and occurs most frequently through loss of the tumor suppressor PTEN or activating mutations in PIK3CA (p110-alpha). Contrary to PIK3CA, which is frequently mutated within hot spots causing increased kinase activity, mutation of PIK3CB is quite rare[355,358-359]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
PIK3R1

ALTERATION
E476*

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
1426G>T

VARIANT ALLELE FREQUENCY (% VAF)
34.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical[360-361] and preclinical[362-363] 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[360], 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[364]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[186,215,363,365-366] or AKT[367-368]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[369].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[16], glioblastoma (GBM; 11%)[370], uterine carcinosarcoma (11%)(cBioPortal, 2021)[75-76], and lower grade glioma (5%)[371]. 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[372-374], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[372]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[375] and metastasis-free survival in breast cancer[376]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[377].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[378]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[379-382], promote tumorigenesis[362,367,379], and promote hyperplasia in the context of PTEN-deficiency[383]. Alterations such as seen here may disrupt PIK3R1 function or expression[240,252,363,368-369,373-374,384-390].

GENE
PTEN

ALTERATION
R130Q, R173H

TRANSCRIPT ID
NM_000314, NM_000314

CODING SEQUENCE EFFECT
389G>A, 518G>A

VARIANT ALLELE FREQUENCY (% VAF)
35.0%, 32.4%

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[221,391-393]. Clinical studies in endometrial cancer have not observed an association between PTEN deficiency and response to the mTOR inhibitors everolimus or temsirolimus[186,394-400]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[401-405], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[406], ovarian cancer[286], uterine leiomyosarcoma[407], and endometrial cancer[405] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[102,408]. 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)[409].

FREQUENCY & PROGNOSIS

PTEN mutation has been observed in 55-65% of endometrial cancers and in 70% of primary endometrioid endometrial cancers, whereas PTEN loss has been reported in 5% of endometrial carcinoma cases[16,410-411]. PTEN mutation or loss has been suggested to play a role in endometrial cancer progression; high PTEN expression has been observed in Grade 1 and 2 tumors but not in Grade 3 tumors[230,412-414]. Loss of PTEN protein expression has been correlated with increased survival of patients with Stage 3 or 4 endometrial carcinoma, but not Stage 1 or 2[230].

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[392]. Alterations such as seen here may disrupt PTEN function or expression[415-455].

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, Mar 2021)[87]. 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[456-457]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[456,458]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[456]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
RAD51D

ALTERATION
R253Q

TRANSCRIPT ID
NM_002878

CODING SEQUENCE EFFECT
758G>A

VARIANT ALLELE FREQUENCY (% VAF)
1.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited preclinical data[459-460] and clinical evidence in ovarian cancer[103,461] indicate that loss or inactivation of RAD51D may confer sensitivity to PARP inhibitors. Loss of functional RAD51D may also predict sensitivity to DNA-damaging drugs such as mitomycin C and cisplatin[459,462-464]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

RAD51D mutation has been observed in 3.1% of endometrioid carcinomas, but not in any samples of other endometrial histologies analyzed in the COSMIC database (Sep 2021)[77]. Published data investigating the prognostic implications of RAD51D alteration in endometrial carcinomas are limited (PubMed, Sep 2021).

FINDING SUMMARY

RAD51D, also known as RAD51L3, is involved in homologous recombination-mediated DNA repair and telomere maintenance[465-468]. Germline mutations in RAD51D have been associated with hereditary breast and ovarian cancer[460,469-472], and RAD51D mutation carriers have an increased lifetime risk of ovarian cancer, estimated to be 10-12%[460,473]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in RAD51D are associated with hereditary breast and ovarian cancer (HBOC) syndrome, an autosomal dominant disorder that predisposes patients to breast and ovarian malignancies[474-475]. The risk of ovarian cancer in RAD51D mutation carriers has been estimated to be 10 to 12%[460,473]. Germline RAD51D mutation has been reported at frequencies of up to 1% in breast and ovarian familial cancer populations without BRCA1/2 mutation[472,476-477]. In the appropriate clinical context, germline testing of RAD51D is recommended.

GENE
TSC1

ALTERATION
Q739*

TRANSCRIPT ID
NM_000368

CODING SEQUENCE EFFECT
2215C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC1 can activate mTOR signaling[478-479]; however, response rates for patients with TSC1-mutated solid tumors treated with MTOR inhibitors such as everolimus and temsirolimus have been low[480-482]. In the prospective NCI-MATCH study, the ORR for patients with various TSC1-mutated solid tumors treated with everolimus was 7.7% (1/13); the single response was reported for a patient with urothelial cancer[480]. In TSC1-mutated renal cell carcinoma (RCC), responses to MTOR inhibitors have been described in multiple case series and reports[178,483-486], but retrospective analysis of a broader cohort showed no responses in TSC1-mutated RCC (0/7)[481]. Retrospective analyses of the RECORD-3, GRANITE-1, and EVOLVE-1 studies of everolimus to treat patients with RCC, gastric cancer, or hepatocellular carcinoma, respectively, showed no significant association between alterations in MTOR, TSC1, or TSC2 and median PFS[482].

FREQUENCY & PROGNOSIS

TSC1 mutations have been reported in 5.2% of endometrial carcinomas analyzed in COSMIC (Sep 2021)[77]. Published data investigating the prognostic implications of TSC1 alterations in endometrial cancer are limited (PubMed, Oct 2020).

FINDING SUMMARY

TSC1 encodes the protein Hamartin, which interacts with Tuberin, the gene product of TSC2, to inhibit and regulate mTOR activity[478,487]. Alterations such as seen here may disrupt TSC1 function or expression[488-490].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC1 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma[491-492]. TSC1 mutations account for approximately 10 to 30% of reported sporadic cases[493]. Prevalence for this disorder in the general population is estimated to be 1/6,000 from birth and 1/12,000 to 1/14,000 in children under 10 years of age[494]. In the appropriate clinical context, germline testing of TSC1 is recommended.

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GENE
APC

ALTERATION
S2307L, R2204*

TRANSCRIPT ID
NM_000038, NM_000038

CODING SEQUENCE EFFECT
6920C>T, 6610C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.6%, 36.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[495]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[496-497]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[498]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrial Carcinoma TCGA dataset, APC mutations are reported in 12% of cases[16]. Studies have reported APC mutations at varying frequencies in endometrial carcinoma, from no mutations being detected in 128 samples to 43% (12/28) of analyzed endometrial carcinomas having APC mutations[499-500]. APC methylation has been detected at a higher frequency in endometrial adenocarcinomas with microsatellite instability (MSI) (43%, 17/40), than in cases without MSI (16%, 12/74)[500-501]. Two studies of endometrial carcinomas have reported the absence of APC protein expression in 8% (2/24) and 71% (30/42) of cases[499,502]. A preclinical study using a mouse model demonstrated that loss of APC could induce endometrial cancer[503]. The prognostic significance of APC mutations in endometrial cancer remains unclear (PubMed, Jul 2021). Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[504].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[505]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Mar 2021)[87]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[506-508]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[509], and in the appropriate clinical context germline testing of APC is recommended.

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GENE
ATRX

ALTERATION
R907*

TRANSCRIPT ID
NM_000489

CODING SEQUENCE EFFECT
2719C>T

VARIANT ALLELE FREQUENCY (% VAF)
30.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical[510-511] and limited clinical data[512], ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT[512]. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan[513], combined PARP and ATR inhibition[511], or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan[514]; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[515]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[515-517], 12.6% of pheochromocytomas and paragangliomas[518], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[519-523]. ATRX loss in PNET[516,524] and melanoma[525] and mutation in other neuroendocrine tumors[518] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[514]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[526-529] and has been proposed as a distinguishing biomarker[527-529]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[520-523]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[527]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[530-531].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[532-533]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[515,531,534-535]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[536-538]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[532,539]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[540].

GENE
CARD11

ALTERATION
R271W

TRANSCRIPT ID
NM_032415

CODING SEQUENCE EFFECT
811C>T

VARIANT ALLELE FREQUENCY (% VAF)
2.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although there are no therapies targeting CARD11 alterations, a number of drugs that block NF-kB activation are under investigation[541-543]. Preclinical evidence from models of mantle cell lymphoma suggests that tumors with CARD11 mutations may exhibit reduced sensitivity to inhibitors of BCR/NF-kB signaling including ibrutinib and lenalidomide[544-545]. CARD11 mutations have also been correlated with reduced sensitivity to sotrastaurin (protein kinase C inhibitor) in preclinical models of DLBCL[546].

FREQUENCY & PROGNOSIS

CARD11 alterations have been most frequently reported in B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL; 11-23%)[547-549], follicular lymphoma (21-25%)[550], primary central nervous system lymphoma (16-30%)[551-552], splenic marginal zone lymphoma (7-9%)[553-554], and mantle cell lymphoma (6%)[544]. CARD11 mutations have also been detected in T-cell lymphomas, specifically in angioimmunoblastic T-cell lymphomas (AITLs), peripheral T-cell lymphomas (PTCLs), and cases of Sezary syndrome[555-557]. Copy number gains and consequent CARD11 overexpression have been reported in 71% (12/17) of patients with aggressive AITL and in 41% (30/73) of patients with PTCL[558-559]. Increased CARD11 expression has also been observed in T-ALL[560]. CARD11 amplification in DLBCL and increased CARD11 protein expression in AITL or PTCL is associated with reduced overall survival[547,559]. Although CARD11 mutations have been detected in a variety of solid tumors[561-566], the prognostic implications of CARD11 alterations in non-hematological malignancies are unclear.

FINDING SUMMARY

CARD11 (also known as CARMA1) is a scaffold protein critical for B- and T-cell receptor-mediated NF-kappaB (NF-kB) activation[567-569]. Activating CARD11 mutations, often occurring within the CARD (aa 18-110) or coiled-coil (aa 130-499) domains, can facilitate constitutive NF-kB signaling, proliferation, and cell survival in lymphomas[548,555,557,569-576]. Preclinical evidence suggests that activating CARD11 mutations may reduce sensitivity to ibrutinib, lenalidomide, and sotrastaurin in lymphoma[544-546]. Some germline CARD11 mutations have been found to underlie B-cell expansion with NF-kB and T-cell anergy (BENTA), a disorder characterized by congenital B-cell lymphocytosis[569,572,577].

GENE
CREBBP

ALTERATION
E50*

TRANSCRIPT ID
NM_004380

CODING SEQUENCE EFFECT
148G>T

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CREBBP. The use of histone deacetylase (HDAC) inhibitors are being investigated in clinical trials that are recruiting patients with either lymphoma or urothelial carcinoma harboring CREBBP alterations. However, it has been reported that there is no correlation between CREBBP mutation status and response to HDAC inhibitors in DLBCL[578].

FREQUENCY & PROGNOSIS

CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 39%) and diffuse large B-cell lymphoma (DLBCL, 17%), and at lower frequency in acute lymphoblastic leukemia (ALL, 6%), and tumors of the urinary tract (15%), skin (11%), endometrium (9%), liver (9%), and stomach (9%) (COSMIC, 2021)[77]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[579], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[580]. Reports have found CREBBP mutation in 62-68% of patients with FL[581-582], which was associated with immune evasion[581]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[583-584].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[585]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[586]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[587-588].

GENE
CTCF

ALTERATION
R129*

TRANSCRIPT ID
NM_001191022

CODING SEQUENCE EFFECT
385C>T

VARIANT ALLELE FREQUENCY (% VAF)
36.3%

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, 2021)[75-76]; 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[589-590].

FINDING SUMMARY

CTCF encodes an 11-zinc-finger protein that is implicated in a number of regulatory roles, including gene activation and repression, imprinting, insulation, methylation, and X chromosome inactivation[591]. CTCF plays a role in transcriptional regulation of a number of key cancer-associated genes, including the oncogene MYC[592] and tumor suppressor TP53[593], via maintenance of local DNA methylation status. The 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 overall survival in epithelial ovarian cancer[594-595].

GENE
CTNNA1

ALTERATION
R451*

TRANSCRIPT ID
NM_001903

CODING SEQUENCE EFFECT
1351C>T

VARIANT ALLELE FREQUENCY (% VAF)
32.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to address genomic alterations in CTNNA1.

FREQUENCY & PROGNOSIS

CTNNA1 mutations have been observed with highest incidence in endometrial carcinoma (6.8%)[596], cutaneous melanoma (6.4%)[597], colorectal adenocarcinoma (4.4%)[596], and stomach adenocarcinoma (4.0%) TCGA datasets (cBioPortal, 2021)[75-76]. CTNNA1 mutations have been observed in patients with hereditary diffuse gastric carcinoma without CDH1 mutations[598-599]. Reduced CTNNA1 expression in patients with breast cancer has been correlated with a poor clinical outcome and breast cancer brain metastasis[600-601]. Deletion and hypermethylation of CTNNA1 has been observed in up to 22% (18/83) of myelodysplastic syndrome (MDS) cases and associated with poor clinicopathological features[602-604] and a trend for inferior survival[602]. Loss of CTNNA1 expression via 5q deletion or hypermethylation has been reported as a frequent event in acute myeloid leukemia and associated with shorter relapse-free survival in one study[604-606].

FINDING SUMMARY

CTNNA1 encodes alpha-catenin, a member of the cadherin family that functions in cell adhesion. Alpha-catenin acts as a tumor suppressor, through mechanisms that can vary by tissue[607-608]. Alpha-catenin is one of three catenin proteins that are in complex with E-cadherin to help mediate cell-cell adhesion in epithelial tumor suppression[607-608]; loss of cell adhesion may contribute to cancer cell invasiveness and formation of metastases. In epidermal cells, alpha-catenin acts as a tumor suppressor by inducing YAP1 phosphorylation and cytoplasmic localization[601,609]. Alpha-catenin also acts as a tumor suppressor by interacting with IKBalpha to influence the NF-KB pathway in E-cadherin-negative basal-like breast cancer cells[601]. Loss of alpha-catenin expression is also hypothesized to alter the balance between the cytoplasmic (cell adhesion) and nuclear (cell proliferation) functions of beta-catenin, further contributing to oncogenesis[610].

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GENE
CUL3

ALTERATION
L602*

TRANSCRIPT ID
NM_003590

CODING SEQUENCE EFFECT
1805T>G

VARIANT ALLELE FREQUENCY (% VAF)
34.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Mutations affecting CUL3-KEAP1 complex formation and regulation of the stress-regulated transcription factor NRF2 have been found in 4/5 cases of sporadic papillary renal cell carcinoma[611]. Mutations affecting the CUL3-KEAP1 complex have also been reported in lung cancer, and linked to increased NF-kB signaling through upregulation of IkkB protein expression[612]. Decreased CUL3 expression has been linked to an aggressive phenotype in bladder cancer models[613] and to formation of hepatocellular carcinomas through regulation of cyclin E expression[614].

FINDING SUMMARY

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

GENE
ESR1

ALTERATION
R256Q

TRANSCRIPT ID
NM_000125

CODING SEQUENCE EFFECT
767G>A

VARIANT ALLELE FREQUENCY (% VAF)
36.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapies that directly target ER-alpha, such as selective ER modulators (SERMs) and the selective ER degrader (SERD) fulvestrant, as well as aromatase inhibitors (AIs) that inhibit estrogen production, are approved to treat ER-positive (ER+) and/or hormone receptor-positive (HR+) breast cancer (NCCN Guidelines v6.2020). AI treatment has also been reported to provide clinical benefit in a subset of HR+ gynecologic malignancies[615-619]. Combinations of fulvestrant and CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib, have also demonstrated efficacy for patients with ESR1-mutated breast cancer[620]. Clinical data suggest that ESR1 mutations may confer sensitivity to the first-generation SERD fulvestrant in breast cancer[621-622]. A retrospective analysis of ESR1 mutations in gynecologic malignancies reported clinical benefit for patients with ESR1 mutations and fulvestrant treatment as a monotherapy or in combination, including 1 patient with peritoneal serous carcinoma and an ESR1 Y537N mutation who experienced prolonged clinical benefit (48+ months) from fulvestrant monotherapy[623]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— Potential Resistance —

Extensive clinical evidence indicates that ESR1 mutations arise primarily during treatment with AIs, especially relative to other ER-targeting therapies, and ESR1 ligand-independent activating alterations may predict lack of benefit from subsequent AI treatment in breast carcinoma[621,624-625]. In gynecologic malignancies, activating ESR1 Y537S and D538G mutations have been reported to confer resistance to AI treatment, particularly for patients who have already received AI treatment[623,626].

FREQUENCY & PROGNOSIS

ESR1 mutation has been reported in 2.5-7.1% of endometrial carcinomas analyzed (COSMIC, cBioPortal, Nov 2020)[75-77]. Lower levels of ER-alpha protein and/or ESR1 mRNA expression have been associated with a reduced survival in endometrial carcinoma[627-628].

FINDING SUMMARY

ESR1 encodes estrogen receptor alpha (ER-alpha), one of the major estrogen receptor isoforms in humans. Along with co-activator proteins, the ER complex promotes transcription of genes involved in cell cycle progression and survival[629]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
FAM123B

ALTERATION
E387*

TRANSCRIPT ID
NM_152424

CODING SEQUENCE EFFECT
1159G>T

VARIANT ALLELE FREQUENCY (% VAF)
35.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in FAM123B.

FREQUENCY & PROGNOSIS

Somatic mutation of FAM123B is rare in most cancers (COSMIC, 2021)[77], but is observed at rates ranging from 5-30% in Wilms tumor[630-632]. No association between FAM123B alteration and clinical features or outcomes of Wilms tumor has been documented.

FINDING SUMMARY

FAM123B, also known as AMER1, encodes the protein WTX, which binds to beta-catenin, enhancing its proteasomal degradation and thereby exerting a repressive effect on WNT pathway signaling[633]. Germline mutation or deletion of FAM123B causes osteopathia striata with cranial sclerosis[634-635].

GENE
KEL

ALTERATION
E494*

TRANSCRIPT ID
NM_000420

CODING SEQUENCE EFFECT
1480G>T

VARIANT ALLELE FREQUENCY (% VAF)
32.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to target genomic alterations in KEL.

FREQUENCY & PROGNOSIS

KEL mutations have been reported in tumors of the skin, lung, endometrium, stomach, large intestine, soft tissue, and liver at rates of 1.9-8.4%; up to 1.2% of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphocytic leukemia-small lymphocytic lymphoma (CLL/SLL) samples (COSMIC, 2021)[77]. However, the mechanism by which KEL mutations contribute to tumor formation is not known.

FINDING SUMMARY

KEL encodes a transmembrane glycoprotein with similarities to zinc-dependent metalloproteases; this glycoprotein is highly polymorphic and forms the Kell blood group antigen[636].

GENE
KLHL6

ALTERATION
D104N

TRANSCRIPT ID
NM_130446

CODING SEQUENCE EFFECT
310G>A

VARIANT ALLELE FREQUENCY (% VAF)
1.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to address genomic alterations in KLHL6.

FREQUENCY & PROGNOSIS

KLHL6 lies in a segment of chromosome 3q that has been observed to exhibit significant amplification in both squamous cell lung[637] and ovarian[638] carcinoma.

FINDING SUMMARY

KLHL6 encodes a protein that exhibits homology to the Drosophila Kelch gene and is hypothesized to play a role in germinal center B-cell differentiation[639]. Whole genome sequencing identified somatic alteration of KLHL6 in a small number of chronic lymphocytic leukemias[640], whereas an exome-sequencing effort identified similar alterations in a follicular lymphoma case[641].

GENE
MAP3K1

ALTERATION
G914*

TRANSCRIPT ID
NM_005921

CODING SEQUENCE EFFECT
2740G>T

VARIANT ALLELE FREQUENCY (% VAF)
33.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MAP3K1.

FREQUENCY & PROGNOSIS

Somatic alterations of MAP3K1, including missense mutations, truncating alterations, and loss of heterozygosity, have been observed most frequently in breast and uterine carcinomas (cBioPortal, COSMIC, 2021)[75-77].

FINDING SUMMARY

MAP3K1 encodes a multifunctional protein kinase and E3 ubiquitin ligase involved in several signal transduction pathways central to cancer cell biology[642]. Different MAP3K1 protein isoforms have been suggested to exert both pro- and anti-apoptotic influences[643-644]. Germline polymorphism in MAP3K1 has been hypothesized to associate with risk for at least some subtypes of breast carcinoma[645], but the extent of effect is small and experimental results have been inconsistently replicated[646].

GENE
MLL2

ALTERATION
R5214C

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
15640C>T

VARIANT ALLELE FREQUENCY (% VAF)
1.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2021)[77], and are especially prevalent in lung squamous cell carcinoma (SCC)[637] and small cell lung carcinoma (SCLC)[647]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[648]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[649]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[650].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[651]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[652]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[653].

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[90-95]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[94,96-97]. 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
MSH6

ALTERATION
E641*

TRANSCRIPT ID
NM_000179

CODING SEQUENCE EFFECT
1921G>T

VARIANT ALLELE FREQUENCY (% VAF)
34.2%

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[28,47,654-657]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[33,658] and nivolumab[659]. Higher mutation burden was also reported to be associated with response to pembrolizumab[23]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[30], 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

MSH6 mutations have been reported in 17% of endometrioid carcinomas[16]. Multiple studies have cited an increased risk (16-44%) of endometrial cancer for female carriers of germline MSH6 mutations[660-662]. Endometrial tumors harboring MMR protein alterations have been associated with worse overall and progression-free survival[663].

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[47]. Alterations such as seen here may disrupt MSH6 function or expression[664-669].

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 hereditary cancer-predisposing syndrome (ClinVar, Mar 2021)[87]. 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[670]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[671]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[672]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[670,673-674]. 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[675-679]. Given the association between MSH6 and these inherited syndromes, in the appropriate clinical context, germline testing of MSH6 is recommended.

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GENE
POLE

ALTERATION
V411L

TRANSCRIPT ID
NM_006231

CODING SEQUENCE EFFECT
1231G>C

VARIANT ALLELE FREQUENCY (% VAF)
34.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address POLE mutations. However, increased mutation load, such as may occur in "ultramutated" cancers harboring deleterious mutations in POLE, has been reported to be associated with response to the anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[15,23] and nivolumab[680-681]. In particular, a patient with non-small cell lung cancer harboring a deleterious POLE mutation achieved durable clinical benefit on pembrolizumab[23]; two patients with POLE-mutated endometrial cancer responded to pembrolizumab[15] or nivolumab[682]; two patients with POLE-mutated, TMB-high, MSS colorectal cancer responded to pembrolizumab[683]; and two patients with biallelic mismatch repair deficiency (bMMRD)-associated glioblastoma harboring POLE mutations experienced clinically and radiologically significant responses to nivolumab[680]. Furthermore, POLE-mutated endometrial cancers have been shown to have higher predicted neoantigen load, increased numbers of tumor-infiltrated lymphocytes (TILs), and higher expression of PD-1 and PD-L1 in the TILs[684], which are potential biomarkers of response to anti-PD-1 immunotherapies.

FREQUENCY & PROGNOSIS

POLE alterations have been reported in 6-15% of endometrial carcinomas (COSMIC, Feb 2021)[18,77,685-686]. In the context of endometrial carcinoma, POLE mutations are associated with high tumor grade[18] and correlate with better prognosis, with the most favorable prognosis seen for high-grade tumors (NCCN Uterine Neoplasms Guidelines, v2.2021)[16,685-689].

FINDING SUMMARY

POLE encodes the catalytic subunit A of DNA polymerase epsilon, which plays roles in DNA replication and repair[690]. Deleterious mutations in POLE, mainly located within the exonuclease domain (amino acids 268–471) and reported at hotspot residues F104, D275, P286, S297, N363, D368, V411, L424, P436, R446, A456, Y458, S459, and S461, are predicted to disrupt the proofreading function of the enzyme, resulting in a high mutation rate and contributing to the development of "ultramutated," microsatellite-stable cancers[16,18,26-28,680-681,691-698].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in POLE underlie polymerase proofreading-associated polyposis (PPAP), a highly penetrant, autosomal-dominant disorder characterized by the development of adenomatous polyps and an increased risk of intestinal, colorectal, and endometrial cancers[26-27,691-692,694,699]. PPAP underlies 0.1% to 0.4% of familial cancers[700]. The lifetime risk of colorectal cancer for a POLE mutation carrier is estimated to be 21% to 28%[701]. In the appropriate clinical context, germline testing of POLE is recommended.

GENE
SETD2

ALTERATION
splice site 5278-1G>T

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
5278-1G>T

VARIANT ALLELE FREQUENCY (% VAF)
35.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[702]. SETD2 has been associated with favorable prognosis in gastric cancer[703]. SETD2 has also been associated with poor prognosis in RCC and MDS[704], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[705] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[706]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[707]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
SPEN

ALTERATION
A2727V

TRANSCRIPT ID
NM_015001

CODING SEQUENCE EFFECT
8180C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address SPEN inactivating mutations. Although gamma-secretase inhibitors are in clinical development to target NOTCH activation, it is not known if these therapies would be beneficial in the context of SPEN mutation.

FREQUENCY & PROGNOSIS

SPEN truncating mutations have been reported in adenoid cystic carcinoma (ACC) (21%)[708] and splenic marginal zone lymphoma (SMZL) (5%)[553]; NOTCH pathway gene mutations were frequent in both ACC and SMZL and observed in approximately 30% of cases[553,708].

FINDING SUMMARY

SPEN (also known as MINT or SHARP) encodes a transcriptional regulator that interacts with HDAC1 and the SMRT/NcoR corepressors[709-710]. SPEN represses the transcriptional activity of the NOTCH signaling pathway[711-712]. Activation of NOTCH signaling results in binding of the transcription factor RBPJ to the NOTCH intracellular domain and consequent activation of the NOTCH transcriptional program[713]. SPEN binding to RBPJ has been shown to repress NOTCH-mediated transcription[711-712]. SPEN alterations that result in loss of the RBPJ-interaction domain (aa 2804-2816)[711-712] or the SPOC domain (aa 3498-3664)[710] are predicted to disrupt binding of SPEN to RBPJ or corepressors and are likely to be inactivating.

GENE
STAG2

ALTERATION
splice site 463-1G>T

TRANSCRIPT ID
NM_006603

CODING SEQUENCE EFFECT
463-1G>T

VARIANT ALLELE FREQUENCY (% VAF)
32.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target STAG2. However, in preclinical studies, STAG2 inactivation by mutation or knockdown resulted in increased sensitivity to PARP inhibitors[714] or oxaliplatin[715].

FREQUENCY & PROGNOSIS

STAG2 mutations have been observed most frequently in urothelial bladder carcinoma (16-35%)[566,716-719], Ewing sarcoma (13-22%)[720-721], upper urinary tract urothelial carcinoma (11%)[722], myeloid malignancies (6%)[723-724], and glioblastoma (6%)[725]. STAG2 truncation mutations are associated with loss of protein expression[716-717,719,721]. In patients with Ewing sarcoma, STAG2 and TP53 mutations often co-occur and are associated with decreased overall survival, although mutation of either STAG2 or TP53 alone was not demonstrated to affect survival[720-721]. STAG2 mutation in patients with myelodysplastic syndrome is associated with decreased overall survival and has also been associated with increased response to treatment with azacitidine or decitabine in patients with myeloid malignancies[723]. The data on the prognostic significance of STAG2 mutation or loss of STAG2 protein expression in the context of urothelial bladder carcinoma are conflicting[716-719]. In patients with pancreatic ductal adenocarcinoma, loss of STAG2 staining was significantly associated with decreased overall survival, but was also associated with survival benefit from adjuvant chemotherapy[715]. An inactivating STAG2 mutation was identified in a patient with melanoma that acquired resistance to vemurafenib and preclinical evidence suggests that loss of STAG2 expression decreases the sensitivity of BRAF V600E-positive melanoma cells to vemurafenib, dabrafenib, and trametinib[726].

FINDING SUMMARY

STAG2 encodes a subunit of the cohesin complex, which maintains sister chromatid cohesion. The cohesin complex includes four subunits: SMC1A, SMC3, RAD21, and either STAG1 or STAG2[727]. Cohesin is also involved in transcriptional regulation, DNA replication and DNA repair[727]. STAG2 mutations, which are mostly truncating, or loss of STAG2 protein expression have been reported in multiple cancer types[727-728]. STAG2 deletion has been shown to promote tumorigenesis in preclinical studies[715], and STAG2 inactivation has been proposed to promote tumorigenesis via a mechanism that involves increased aneuploidy[716,718,725] or altered transcriptional regulation[717,719,723-724].

GENE
TNFAIP3

ALTERATION
R87*

TRANSCRIPT ID
NM_006290

CODING SEQUENCE EFFECT
259C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that address the loss of TNFAIP3. A20 has multiple functions and is subject to a wide range of genomic lesions, thereby making it challenging to develop a unified therapeutic approach. Potential avenues targeting dysregulation of ubiquitination pathways include anti-CD20 therapies, such as rituximab, and proteasome inhibitors, such as bortezomib[729].

RNAi-mediated downregulation of TNFAIP3 has been reported to sensitize multiple myeloma cells to bortezomib[730].

FREQUENCY & PROGNOSIS

In the COSMIC dataset, TNFAIP3 mutations have been reported in 3.5% of prostate, 3.1% of endometrial, 2.8% of skin, 2.7% of gastric, and 2.4% of large intestine cancers (Jan 2021)[77]. Overexpression of TNFAIP3 has been associated with aggressive high-grade ER-/PR-negative breast tumors[731], resistance to TNF-alpha and TRAIL-induced apoptosis in glioblastoma[732-733] and to chemotherapy in acute lymphoblastic leukemia[734], and poor prognosis in adrenocortical carcinoma[735]. Loss of heterozygosity in the genomic region including TNFAIP3 has been found in 16.8% (25/149) of colorectal adenocarcinomas, and significantly decreased TNFAIP3 mRNA expression has been observed in colorectal cancer (CRC) tumors compared with adjacent non-neoplastic mucosa[736]. Reduced A20 expression has been suggested as a marker of poor prognosis in CRC[737].

FINDING SUMMARY

TNFAIP3 encodes tumor necrosis factor alpha-induced protein 3, also known as A20, a regulator of NF-kB signaling and apoptosis[738] that has both ubiquitin ligase and deubiquitinase activities[739-740] and whose loss or inactivation may be tumorigenic[741]. TNFAIP3 is frequently deleted or mutated in lymphoma, where it functions as a tumor suppressor[741], but its expression and function are context dependent in solid tumors[738,742-745], leukemia[734,746-747], and multiple myeloma[748-749]. TNFAIP3 mutations that disrupt the A20p37 chain (amino acids 371–790), which mediates ubiquitin ligase activity and interaction with the cIAP1/TRAF2 complex[739,750], are predicted to be inactivating. In T-cells, cleavage of A20 codon R439 by MALT1 has been shown to upregulate NFkB signaling; R439A has been shown to block MALT1-mediated NF-kB activation[751]; however, the function of R439 mutations outside of the context of T-cell lymphoma has not been reported.

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GENE
TP53

ALTERATION
F113V - subclonal, T211A

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
337T>G, 631A>G

VARIANT ALLELE FREQUENCY (% VAF)
0.77%, 36.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[752-755], or p53 gene therapy and immunotherapeutics such as SGT-53[756-760] and ALT-801[761]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[762]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[763]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[764]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[765]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[766]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[767]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[760]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[768]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[769-771]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[772]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[73,773]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[774-775]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 29% of endometrial carcinomas analyzed in COSMIC, including 60% of serous carcinomas, 36% of clear cell carcinomas, and 23% of endometrioid carcinomas (Feb 2021)[77]. In one large study, high (pathologic) expression of p53 was found in 24% of endometrial carcinoma samples and was associated with non-endometrioid histology, high grade (Grade 3 vs. Grade 1-2), and advanced FIGO stage, as well as with lymph node metastasis and poor disease-specific survival, but was not an independent factor for poor prognosis in multivariate analysis[776]. In other studies, p53 alterations (defined as TP53 mutation or p53 nuclear expression) have been found to be associated with poor prognosis in patients with endometrial cancer[777-778].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[779]. Alterations such as seen here may disrupt TP53 function or expression[780-784].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[785-787], including sarcomas[788-789]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[790] to 1:20,000[789]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[791]. In the appropriate clinical context, germline testing of TP53 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[90-95]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[90-91]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[792]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[94,96-97]. 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
XPO1

ALTERATION
R749Q

TRANSCRIPT ID
NM_003400

CODING SEQUENCE EFFECT
2246G>A

VARIANT ALLELE FREQUENCY (% VAF)
0.90%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

XPO1 activation may predict sensitivity to XPO1 inhibitors[793], such as the selective inhibitors of nuclear export (SINEs)[794] KPT-330[795] and KPT-8602[796-797], which are in clinical trials in solid tumors and hematological cancers. In a Phase 1 trial of KPT-330 for unselected advanced solid tumors, one of 157 evaluable patients achieved a complete response, six achieved partial responses (4%), and 67 (43%) achieved stable disease (SD), which was durable for ≥4 months for 27 patients (17%)[798]. A patient with accelerated-phase chronic myelogenous leukemia (CML) refractory to available tyrosine kinase inhibitors demonstrated short-term anti-leukemic activity from KPT-330[799]. Inhibitors of XPO1 have shown efficacy in mouse models and cultured cells of CML, T-cell acute lymphoblastic leukemia, acute myeloid leukemia, mantle cell lymphoma, multiple myeloma, and CLL[795,797,799-804], as well as in GIST, a subset of sarcomas[805], and ESCCs[806].

FREQUENCY & PROGNOSIS

XPO1 mutations have been reported at highest frequency in chronic lymphocytic leukemia (2-15%) and endometrial tumors (3-5%) and at lower incidences in other tumor types (COSMIC, 2021)[16,77,640,807-809]. One study reported XPO1 mutation at high frequency in cases of Hodgkin lymphoma (26%, 5/19) and primary mediastinal B-cell lymphoma (24%, 28/117)[810]. In CLL, XPO1 correlates with unmutated IGHV status, presence of NOTCH1 mutations, increased white blood cell count, and decreased progression-free survival after certain chemoimmunotherapy regimens[640,807,809,811]. Increased levels of nuclear exportin-1 have been reported to correlate with clinical stage in human cholangiocarcinoma samples, and reduced exportin-1 expression suppressed tumor growth in a xenograft model of the disease[812].

FINDING SUMMARY

XPO1 encodes exportin-1, also known as CRM1, a nuclear pore protein that controls nuclear export and localization of multiple cell cycle- and proliferation-associated proteins[813]. Exportin-1 may also be required for efficient centrosome maintenance by BRCA1[814]. XPO1 residue E571 is a mutational hotspot in chronic lymphocytic leukemia (CLL) and other tumor types[640,807,809-811,815], although mutations at this site have not been functionally characterized. XPO1 D624G has been reported in the context of esophageal squamous cell carcinoma (ESCC) and has been suggested to lead to gain of function[806].

GENE
ZNF217

ALTERATION
D326N

TRANSCRIPT ID
NM_006526

CODING SEQUENCE EFFECT
976G>A

VARIANT ALLELE FREQUENCY (% VAF)
34.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha[816-817]. ZNF217 overexpression has also been associated with resistance to paclitaxel[818] and doxorubicin[819] in breast cancer cell lines. ZNF217 has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells[820].

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[821], ovarian[822-823], gastric[824-825], colon[826], prostate[827], esophageal[828], and urothelial carcinomas[829], glioblastoma[830], and ovarian carcinosarcomas[831]. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that may contribute to tumorigenesis[832-834], and increased expression or activation of ERBB3[821,835], FAK[821], Aurora kinase A[818], AKT[819], and TGF-beta/SMAD signaling[821] has been demonstrated in ZNF217-expressing tumors or cells.

FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression[819,836]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[837]. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture[838-839].

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Dostarlimab

Assay findings association

Tumor Mutational Burden
372 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[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

Single-agent dostarlimab has been approved to treat patients with mismatch repair deficient (dMMR) endometrial cancer based on results observed in the Phase 1 GARNET study. In the study, dostarlimab elicited an ORR of 42% (30/71; 9 CRs, 21 PRs) for patients with endometrial cancer; median PFS, median OS, and median duration of response (DOR) have not been reached[841]. In a Phase 2 study of combination niraparib and dostarlimab for patients with endometrial cancer, patients experienced an ORR of 14% (3/22) and a DCR of 32%, while patients treated with niraparib experienced an ORR of 4.0% (1/23) and a DCR of 20%[842].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

In the Phase 3 KEYNOTE-775 study, combination pembrolizumab and lenvatinib treatment improved median PFS (mPFS, 7.2 vs. 3.8 months, HR=0.56) and median OS (mOS, 18.3 vs. 11.4 months, HR=0.62) for patients with advanced endometrial cancer and prior platinum chemotherapy, compared with physician's choice of chemotherapy; benefit was observed in both mismatch repair deficient (dMMR, mPFS HR=0.36, mOS HR=0.37) and proficient (pMMR, mPFS HR=0.60, mOS HR=0.68) subgroups[843]. Similar results for pembrolizumab with lenvatinib were reported in the Phase 1b/2 KEYNOTE-146 study, with a trend toward an improved ORR for patients who were dMMR compared with pMMR (64% vs. 37%) but a similar ORR for patients who were PD-L1 positive (CPS ≥1.0%) compared with PD-L1 negative (36% vs. 40%)[844]. Single-agent pembrolizumab elicited clinical benefit for 26% (3/23 PRs and 3/23 SDs) of patients with advanced PD-L1-positive (CPS ≥1.0%) endometrial cancer included in the Phase 1b KEYNOTE-028 study, with a mPFS of 1.8 months[845]. In the Phase 2 KEYNOTE 158 multi-solid tumor trial, treatment with the PD-1 inhibitor pembrolizumab led to improved ORR for patients with TMB of 10 Muts/Mb or higher compared those with TMB <10 Muts/Mb (28.3% [34/120] vs. 6.5% [41/635])[11]. In the KEYNOTE 028/012 pan-solid tumor trials, a similar improvement in ORR was reported for patients with >103 non-synonymous mutations/exome (~ equivalency >8 Muts/Mb as measured by this assay) compared to those with <103 non-synonymous mutations/exome (30.6% [11/36] vs. 6.5% [5/77])[4]. A patient with PD-L1-positive, ultramutated endometrial adenocarcinoma harboring POLE mutation experienced a PR to pembrolizumab for more than 14 months[15].

Atezolizumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840], 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[2-3].

SUPPORTING DATA

In a Phase 1 study of single-agent atezolizumab, patients with advanced or recurrent uterine cancer achieved an ORR of 13.3% (2/15), a median PFS of 1.4 months, and a median OS of 9.6 months; both objective responses occurred in PD-L1-positive patients (≥ 5% of immune cells), and one of these patients was also MSI-High[846]. 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%)[12]. Atezolizumab has been studied primarily for the treatment of non-small cell lung cancer (NSCLC)[847-852] and urothelial carcinoma[853-856]. A study of atezolizumab as monotherapy for patients with advanced solid tumors reported a median PFS of 18 weeks and an ORR of 21%, including confirmed responses in 25.6% (11/43) of melanomas, 12.5% (7/56) of renal cell carcinomas (RCC) and 16.7% (1/6) of colorectal cancers (CRCs)[852]. As single-agent therapy in genomically unselected young patients (<30 years old) with relapsed or refractory cancers, atezolizumab elicited an ORR of 1.5% (1/67) for patients with solid tumors, with similar safety and pharmacokinetics as seen in adults[857]. A Phase 1a study of atezolizumab reported an ORR of 14.5% (9/62), a median PFS of 5.6 months, and a median OS of 28.9 months for patients with clear cell RCC[858]. A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 41.7% (10/24) of patients; no dose-limiting toxicities were observed[859]. A Phase 1b study that evaluated atezolizumab in combination with the MEK inhibitor cobimetinib for advanced solid tumors reported an ORR of 8.3% (7/84) in patients with CRC, 40.9% (9/22) in patients with melanoma, 17.9% (5/28) in patients with NSCLC, and 18.8% (3/16) in patients with other tumors (ovarian cancer, clear-cell sarcoma, and RCC); there was no association between BRAF or KRAS mutation status and response rate in any disease setting, and no dose-limiting toxicities were encountered[860-861].

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Avelumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

In a Phase 2 trial of avelumab in recurrent endometrial cancer, patients with MMR deficiency or POLE mutation achieved an ORR of 26.7% (4/15) and a median PFS of 4.4 months; for patients with MMR-proficient tumors, the ORR was 6.2% (1/16) and the median PFS was 1.9 months[862]. The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[863], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[864], urothelial carcinoma[865], mesothelioma[866], ovarian carcinoma[867], and breast cancer[868], and from avelumab combined with axitinib in renal cell carcinoma[869]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[863,867-868] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[870-872] .

Cemiplimab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of endometrial cancer are limited (PubMed, May 2021). 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[873]. 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[874-875] . 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[876].

Durvalumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

The PHAEDRA Phase 2 trial of durvalumab in advanced endometrial cancer reported an ORR of 43% and a DCR of 66% (5 CRs, 10 PRs, 8 SDs in 35 patients) for the MMR-deficient cohort, and an ORR of 3% and a DCR of 29% (1 PR, 9 SDs in 35 patients) for the MMR-proficient cohort using iRECIST criteria[877]. A Phase 2 study for patients with endometrial carcinoma and carcinosarcoma evaluated durvalumab with or without tremelimumab and reported ORR of 14.8% (4/27 with 1 CR and 3 PRs) versus 11.1% (3/27 with 2 CRs and 1 PR), median PFS of 7.6 weeks versus 8.1 weeks, and median duration of response of 16 weeks versus 8 weeks[878].

Everolimus

Assay findings association

FBXW7
R441W

PIK3CA
R88Q, T1025A

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[150], renal cell carcinoma[58], and cervical squamous cell carcinoma[879], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus. On the basis of clinical evidence[178,210-216] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[213-216,880-884] .

SUPPORTING DATA

Clinical benefit has been reported for several patients with PIK3CA-mutated endometrial cancer treated with everolimus as a single agent[186,212,399] or combined with hormone therapy[186,254] . In a Phase 2 clinical trial of recurrent endometrial cancer, 43% (12/28) of patients reported SD at 8 weeks and 21% (6/28) of patients achieved clinical benefit at 20 weeks upon administration of everolimus monotherapy[400]. Combination with the aromatase inhibitor letrozole for the same disease population achieved an ORR of 31% (11/35), with 9 CRs[254]. Further addition of metformin to this regimen led to a clinical benefit rate (CR+PR+SD) of 67% (32/48), including PR in 29% (14/48) of cases; no significant difference was observed between cases with and without KRAS mutation[765]. Everolimus achieved PR or SD in 35% of patients with recurrent endometrial carcinoma; KRAS mutation was associated with reduced median PFS (3.1 vs. 1.0 months) and median OS (9.3 vs. 2.3 months)[399]. Another study investigating estrogen and/or progesterone receptor-positive gynecologic or breast malignancies featuring mutation or loss of genes in the PI3K-AKT-mTOR pathway, including PIK3CA, AKT1, or PTEN, observed SD in 17% (1/6) of patients with endometrial cancer following combined treatment with everolimus and anastrozole[885]. No response was seen in a patient with endometrial stromal sarcoma and Peutz-Jeghers Syndrome associated with a germline STK11 mutation treated with a combination of everolimus and anastrozole[886]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[184], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[185].

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Niraparib

Assay findings association

ATM
R250*

BRCA2
E1879D

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[53-55,887] , colorectal cancer[57], breast cancer[57], gastric cancer[56], cholangiocarcinoma[59], and papillary renal cell carcinoma[58]. On the basis of clinical evidence in ovarian and breast cancers[101-102,888] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

In a Phase 2 study of niraparib for patients with endometrial cancer, patients experienced an ORR of 4.0% (1/23) and a DCR of 20%, while patients treated with niraparib and dostarlimab experienced an ORR of 14% (3/22) and a DCR of 32%[842]. Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[101]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[102]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[889].

Nivolumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,840] , 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[2-3] .

SUPPORTING DATA

A Phase 2 study of cabozantinib combined with nivolumab reported improved median PFS (5.3 vs. 1.9 months) and ORR (25% [9/36] vs. 16.7% [3/18]) compared with nivolumab monotherapy for patients with endometrial cancer; OS was also improved with combination therapy (13.0 vs. 7.9 months), although the data have not matured yet[890]. A retrospective analysis of patients with recurrent and refractory endometrial cancer treated with nivolumab alone or in combination with other agents reported a CR of >20 months for a patient treated with nivolumab and everolimus and an overall clinical benefit rate of 75% (9/12), including 8 SDs of >3 months[891]. A case study reported 2 PRs to nivolumab for patients with endometrial carcinoma harboring high tumor mutation burden; response was ongoing at 7-9 months[682]. Nivolumab monotherapy has been reported to elicit clinical benefit for patients with multiple types of solid tumors, including melanoma (27–31% ORR)[892-896] , non-small cell lung carcinoma (NSCLC; 17–20% ORR and 9–10 months mOS in unselected patients)[897-903] , urothelial carcinoma (20–26% ORR in unselected patients)[904-905] , renal cell carcinoma (RCC; 26% ORR)[906-911] , MSI-High colorectal cancer (CRC; 58% ORR)[912-914] , head and neck squamous cell carcinoma (11–17% ORR)[915-917] , ovarian cancer (6–15% ORR)[918-920] , small cell lung cancer (SCLC; 10–12% ORR)[866,921-922] , gastroesophageal carcinoma (12–18% ORR)[923-925] , and cancer of unknown primary (CUP; 10% ORR in unselected, previously treated patients)[888], as well as with Hodgkin lymphoma (66–87% ORR)[926-928] . Combination treatment with nivolumab plus the CTLA-4 inhibitor ipilimumab has achieved further efficacy in melanoma (up to 61% ORR; mOS > 60 months for the combination vs. 37 months for nivolumab monotherapy)[892,929-931] , NSCLC (17 months mOS)[932], MSI-High CRC (64% ORR)[933], RCC (42% ORR)[934-935] , SCLC (19–25% ORR)[866,922] , urothelial carcinoma (38% ORR in unselected patients; 58% ORR in patients with ≥1% tumor PD-L1 expression)[904], and other solid tumors. Combinations of nivolumab with various targeted therapies, such as pazopanib (1a PR in a patient with epithelioid sarcoma)[936], sunitinib (9% ORR in unselected patients with sarcoma)[937], cabozantinib (29% ORR in patients with immunotherapy-refractory urothelial carcinoma)[938], or vemurafenib (1a durable PR in a patient with BRAF V600E-mutated and PD-L1 positive anaplastic thyroid cancer)[939], have also shown evidence of efficacy and continue to undergo clinical investigation.

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Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
372 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,940] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

A Phase 2 trial treating patients with rare gynecological malignancies with combination nivolumab and ipilimumab reported objective responses in 27% (11/41) of patients, including those with vaginal SCC, ovarian and uterine carcinosarcoma, uterine serous cancer, uterine clear cell carcinoma, and uterine leiomyosarcoma[941].

Olaparib

Assay findings association

ATM
R250*

BRCA2
E1879D

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[53-55,887] , colorectal cancer[57], breast cancer[57], gastric cancer[56], cholangiocarcinoma[59], and papillary renal cell carcinoma[58]. On the basis of extensive clinical evidence in ovarian cancer[107-111] as well as strong clinical evidence in multiple other cancer types[53,98-99,107,110,114,942] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

A heavily pretreated patient with low-grade endometrioid endometrial adenocarcinoma and germline and somatic BRCA2 mutations experienced ongoing SD for 15 months from single-agent olaparib[943]. A patient with high-grade serous endometrial cancer harboring a somatic BRIP1 frameshift alteration experienced a CR following olaparib monotherapy[944]. A patient with endometrial adenocarcinoma and PTEN loss experienced clinical benefit for 8 months following olaparib therapy. Although BRCA alterations were not detected, only a subset of common BRCA mutations were assessed, and the authors could not exclude the possibility of other BRCA alterations contributing to the response[405]. Olaparib has been studied primarily for the treatment of ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[107,110] ; higher response rates have also been observed for patients with platinum-sensitive versus platinum-resistant cancer[109-110,112,945] . As maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib has demonstrated significantly improved median PFS and median OS compared with placebo in the Phase 3 SOLO-1 study[113] and in multiple later-phase studies[105-106,946-947] . Phase 3 studies of olaparib for patients with BRCA-mutated metastatic breast[100] or pancreatic cancer[114] or for patients with metastatic castration-resistant prostate cancer and BRCA or ATM alterations[948] have also reported significantly longer median PFS compared with chemotherapy, placebo, or hormone therapy. Additionally, olaparib has demonstrated clinical activity for patients with other solid tumors harboring BRCA mutations, including leiomyosarcoma[949], cholangiocarcinoma[950], and bladder cancer[951] in smaller studies. Olaparib in combination with the AKT inhibitor capivasertib has demonstrated clinical benefit for patients with solid tumors; a Phase 1 trial reported a 45% (25/56) DCR, including 14 PRs and 11 SDs, and 14 of those experiencing clinical benefit had germline BRCA1/2 mutated-solid tumors[952]. In a Phase 2 study of olaparib plus pembrolizumab for patients with advanced solid tumors, those with BRCA1 or BRCA2 mutations and those with homologous recombination deficient tumors reported the highest ORRs of 29% (6/21) and 21% (16/76), respectively. Patients with homologous recombination repair deficient tumors, including and excluding patients with BRCA1/2 mutations, reported lower ORRs of 15% (8/53) and 6.3% (2/32), respectively[953].

Rucaparib

Assay findings association

ATM
R250*

BRCA2
E1879D

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[53-55,887] , colorectal cancer[57], breast cancer[57], gastric cancer[56], cholangiocarcinoma[59], and papillary renal cell carcinoma[58]. On the basis of strong clinical evidence in ovarian cancer[103-104,763] , as well as clinical data in other cancer types[104,954-955] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of endometrial cancers are limited (PubMed, May 2021). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months).

Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[103]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[763]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[104]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[954]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[955]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[956]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[957]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[958].

Selumetinib

Assay findings association

NF1
R1362*, R2450*

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[169-172,959-963] , glioma[172-176,964] , and non-small cell lung cancer[177], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

A Phase 2 study evaluating selumetinib in patients with recurrent endometrial cancer who had received prior treatment with 1-2 therapies did not reach its primary endpoints of efficacy and 6-month event-free survival, reporting mPFS of 2.3 months and mOS of 8.5 months with 1 CR and 2 PR observed in 52 patients[965]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[170,959-960] and a Phase 1 study[169]. Phase 2 studies reported clinical responses in low-grade glioma[173,966] , melanoma[967-971] , and in lung[177,972-973] and endometrial cancer[965]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[974]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[975]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[976]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[977], docetaxel or dacarbazine[978], AKT inhibitors[979], or cixutumumab (an anti-IGF-1R antibody)[980] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Talazoparib

Assay findings association

ATM
R250*

BRCA2
E1879D

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[53-55,887] , colorectal cancer[57], breast cancer[57], gastric cancer[56], cholangiocarcinoma[59], and papillary renal cell carcinoma[58]. On the basis of strong clinical data in breast cancer[981-983] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[984-987] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

A Phase 1 study reported a PR for a patient with uterine carcinoma and a BRCA2 germline mutation treated with talazoparib plus carboplatin and paclitaxel followed by talazoparib monotherapy[988]. Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[982-983] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[57]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[984-986,989] .

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Temsirolimus

Assay findings association

FBXW7
R441W

PIK3CA
R88Q, T1025A

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[150], renal cell carcinoma[58], and cervical squamous cell carcinoma[879], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus. On the basis of clinical evidence[178,210-216] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[213-216,880-884] .

SUPPORTING DATA

In a pooled analysis, 14% (3/21) of patients with PIK3CA-mutated endometrial cancer treated with temsirolimus or ridaforolimus achieved objective response and 29% (6/21) experienced disease progression[396]. A case report described a patient with heavily pretreated PIK3CA-mutated endometrial cancer who had SD for 17 months with temsirolimus alone followed by combination with letrozole[990]. A Phase 2 clinical trial of temsirolimus in recurrent or metastatic endometrial cancer reported PR in 4/29 (14%) chemotherapy-naïve patients and 4% (1/25) of chemotherapy-treated patients, with SD reported in 69% (20/29) of chemotherapy-naïve patients and 48% (12/25) of chemotherapy-treated patients; however, response in this study was found to be independent of molecular markers of PI3K-AKT-mTOR pathway activation[395]. Another Phase 2 study of temsirolimus in patients with endometrial cancer reported PFS of >15 months in 6 patients and associated clinical benefit and longer PFS with mutation of AKT1 or CTNNB1, respectively[991]. Temsirolimus combined with carboplatin and paclitaxel achieved objective partial responses in 82% (9/11) of patients with endometrial cancer[992]. A Phase 2 trial of temsirolimus in combination with bevacizumab in patients with endometrial carcinoma reported clinical response in 25% of patients[993].

Trametinib

Assay findings association

NF1
R1362*, R2450*

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[169-172,959-963] , glioma[172-176,964] , and non-small cell lung cancer[177], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Although very little clinical data has been reported on the use of MEK inhibitors in endometrial or uterine cancer, a Phase 1 trial of trametinib in combination with an AKT inhibitor (GSK2141795), reported 3/3 objective responses in uterine/endometrial tumors, with 2 patients achieving stable disease (SD) and 1 partial response (PR) occurring in a patient with mutant KRAS and PTEN loss[994]. In other solid tumor types, a Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[995]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[996-997] . A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in patients with pancreatic or salivary gland cancer[998]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status[999]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[184], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[185].

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

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

BIOMARKER

Tumor Mutational Burden

RATIONALE

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

RESULT

372 Muts/Mb

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Missouri, Connecticut, Texas

NCT04589845

PHASE 2

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

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT04181788

PHASE 1/2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Nanjing (China), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chongqing (China), Beijing (China), Chuo-ku (Japan), Kopeysk (Russian Federation)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagoya (Japan), Koto ku (Japan), Singapore (Singapore), Tel Aviv (Israel), Zurich (Switzerland), Rozzano (Italy), Barcelona (Spain), Hospitalet de LLobregat (Spain)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Amsterdam (Netherlands), Napoli (Italy), Roma (Italy), Villejuif Cedex (France), Barcelona (Spain)

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), Beijing (China), Chiyoda-Ku, Tokyo (Japan), North Ryde (Australia), Moscow (Russian Federation), Hod Hasharon (Israel), Drammen (Norway), Glostrup (Denmark)

NCT03192345

PHASE 1

A First-in-human Study of the Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity of SAR439459 Monotherapy and Combination of SAR439459 and Cemiplimab in Patients With Advanced Solid Tumors

TARGETS
PD-1, TGF-beta

LOCATIONS: Taipei 100 (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Heidelberg West (Australia), Melbourne (Australia), Tallinn (Estonia), Hannover (Germany), Essen (Germany), Utrecht (Netherlands)

NCT04261439

PHASE 1

A Phase I/Ib Study of NIZ985 Alone and in Combination With Spartalizumab

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Chuo ku (Japan), Essen (Germany), Napoli (Italy), Leuven (Belgium), Barcelona (Spain), California, Texas

NCT03565445

PHASE 1

A Study of ASP1948, Targeting an Immune Modulatory Receptor, in Subjects With Advanced Solid Tumors

TARGETS
PD-1, NRP1

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Tokyo (Japan), Chiba (Japan), Meldola (Italy), Modena (Italy), Newcastle upon Tyne (United Kingdom), Monza (Italy), Milano (Italy), Glasgow (United Kingdom)

NCT03799003

PHASE 1

A Study of ASP1951 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, TNFRSF18

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Daegu (Korea, Republic of), Chungcheongbukdo (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Washington, California, Nevada

GENE
ATM

ALTERATION
R250*

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

NCT04269200

PHASE 3

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

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), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT04716686

PHASE 2

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

TARGETS
PARP

LOCATIONS: Jinan (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03188965

PHASE 1

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

TARGETS
ATR

LOCATIONS: Sunto (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore), St. Gallen (Switzerland), Bellinzona (Switzerland), Newcastle Upon Tyne (United Kingdom), Genève (Switzerland), Sutton (United Kingdom), Edmonton (Canada)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

GENE
BRCA2

ALTERATION
E1879D

RATIONALE
BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors or to ATR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04269200

PHASE 3

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

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), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT04716686

PHASE 2

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

TARGETS
PARP

LOCATIONS: Jinan (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03188965

PHASE 1

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

TARGETS
ATR

LOCATIONS: Sunto (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore), St. Gallen (Switzerland), Bellinzona (Switzerland), Newcastle Upon Tyne (United Kingdom), Genève (Switzerland), Sutton (United Kingdom), Edmonton (Canada)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

GENE
CTNNB1

ALTERATION
K335T

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03008408

PHASE 2

Phase II Ribociclib, Everolimus and Letrozole in Endometrial Cancer

TARGETS
Aromatase, mTOR, CDK4, CDK6

LOCATIONS: Texas

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

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

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

Electronically signed by Douglas Lin, M.D. | 28 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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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

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

GENE
FANCL

ALTERATION
splice site 904-2A>C

RATIONALE
On the basis of clinical evidence in ovarian cancer, FANCL loss or inactivation may confer sensitivity to PARP inhibitors.

NCT04269200

PHASE 3

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

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), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT04716686

PHASE 2

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

TARGETS
PARP

LOCATIONS: Jinan (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

NCT04159155

PHASE 2/3

A Study of Various Treatments in Serous or p53 Abnormal Endometrial Cancer

TARGETS
PARP

LOCATIONS: Toronto (Canada)

GENE
FBXW7

ALTERATION
R441W

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT02397083

PHASE 2

Phase II Study of Intrauterine Device (IUD) Alone or in Combination With Everolimus in Endometrial Cancer

TARGETS
mTOR

LOCATIONS: Colorado, Michigan, Virginia, Texas

NCT03008408

PHASE 2

Phase II Ribociclib, Everolimus and Letrozole in Endometrial Cancer

TARGETS
Aromatase, mTOR, CDK4, CDK6

LOCATIONS: Texas

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

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

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

GENE
FGFR2

ALTERATION
N549D

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR2.

NCT04865289

PHASE 3

Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9 / MK-7902-001) -China Extension Study

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

LOCATIONS: Hangzhou (China), Shanghai (China), Nanchang (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China), Wuhan (China), Nanning (China), Chongqing (China)

NCT02450136

PHASE NULL

Single-arm Study to Evaluate the Safety and Efficacy of Pazopanib, in Subjects With FGFR2 Amplification, FGFR2 Mutation Refractory Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Innsbruck (Austria), Essen (Germany), Bologna (Italy), Naples (Italy), Leuven (Belgium), Brussels (Belgium), Ghent (Belgium), Washington, Barcelona (Spain), Madrid (Spain)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4

LOCATIONS: Colorado, Minnesota, Arizona, Florida

Electronically signed by Douglas Lin, M.D. | 28 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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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

NCT02272998

PHASE 2

Ponatinib for Patients Whose Advanced Solid Tumor Cancer Has Activating Mutations Involving the Following Genes: FGFR1, FGFR2, FGFR3, FGFR4, RET, KIT.

TARGETS
ABL, FGFRs, FLT3, KIT, RET, VEGFRs

LOCATIONS: Ohio

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, FGFR2, FGFR3, FLT3, LCK, LYN, SRC, VEGFRs, PD-1

LOCATIONS: Villejuif (France)

NCT01543763

PHASE 1

Phase I Tolerability, Efficacy, and Safety Study of Pazopanib in Combination With PCI-24781 in Patients With Metastatic Solid Tumors

TARGETS
HDAC, FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: California

GENE
NF1

ALTERATION
R1362*, R2450*

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), Texas

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT04800822

PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
SHP2, ROS1, ALK, BRAF, EGFR, MEK

LOCATIONS: California, Michigan, New York, Tennessee, Texas

NCT02397083

PHASE 2

Phase II Study of Intrauterine Device (IUD) Alone or in Combination With Everolimus in Endometrial Cancer

TARGETS
mTOR

LOCATIONS: Colorado, Michigan, Virginia, Texas

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

GENE
PIK3CA

ALTERATION
R88Q, T1025A

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845

PHASE 2

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

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881

PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

Electronically signed by Douglas Lin, M.D. | 28 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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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

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Alaska, Washington

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

GENE
PIK3CB

ALTERATION
R321Q

RATIONALE
Preclinical evidence suggests that overexpression of PIK3CB promotes cellular transformation, and that PTEN-deficient cancers may be dependent on PIK3CB for growth. Therefore, inhibitors of PIK3CB or downstream pathway components including AKT may be beneficial in tumors harboring PIK3CB alterations. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04001569

PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Alaska, Washington

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NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT02397083

PHASE 2

Phase II Study of Intrauterine Device (IUD) Alone or in Combination With Everolimus in Endometrial Cancer

TARGETS
mTOR

LOCATIONS: Colorado, Michigan, Virginia, Texas

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

GENE
PIK3R1

ALTERATION
E476*

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.

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, Texas

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
R130Q, R173H

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.

NCT04269200

PHASE 3

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04716686

PHASE 2

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

TARGETS
PARP

LOCATIONS: Jinan (China)

NCT04001569

PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

GENE
RAD51D

ALTERATION
R253Q

RATIONALE
Inactivation of RAD51D may predict sensitivity to PARP inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04269200

PHASE 3

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

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), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT04716686

PHASE 2

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

TARGETS
PARP

LOCATIONS: Jinan (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

NCT04159155

PHASE 2/3

A Study of Various Treatments in Serous or p53 Abnormal Endometrial Cancer

TARGETS
PARP

LOCATIONS: Toronto (Canada)

GENE
TSC1

ALTERATION
Q739*

RATIONALE
Inactivating TSC1 alterations may lead to increased mTOR activation and predict sensitivity to mTOR inhibitors.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT02397083

PHASE 2

Phase II Study of Intrauterine Device (IUD) Alone or in Combination With Everolimus in Endometrial Cancer

TARGETS
mTOR

LOCATIONS: Colorado, Michigan, Virginia, Texas

NCT03008408

PHASE 2

Phase II Ribociclib, Everolimus and Letrozole in Endometrial Cancer

TARGETS
Aromatase, mTOR, CDK4, CDK6

LOCATIONS: Texas

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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.

ABL1
V43fs*4

AKT3
L277R, R241W, V419A and splice site 697-2A>C

ALK
N285Y

APC
L2136I, L23F and L2574I

AR
A871V, D551E and Y364D

ARID1A
G851D

ASXL1
E824D, G1401E and R394H

ATM
E2052K and R493C

ATR
E254D, L108P, R1300C, R635Q and S1701Y

ATRX
D1875Y, K467Q, R701H and T480R

BAP1
D608N

BCOR
E27K, L1334V and V293I

BCORL1
R1226H, S244L and S663Y

BRAF
R389C

BRCA1
D749Y

BRCA2
E1455_E1456>DK, E2020K, L3317R, N1316H and T3414A

BRD4
S499L

BRIP1
L892I and R356Q

BTK
L23I, R13*, R288W and T33I

C11ORF30 (EMSY)
E924K and S335N

CARD11
E420D and P567L

CASP8
E311D

CBFB
A99T

CBL
E394G and R462Q

CCND2
K71T

CDK12
K726T

CDK6
R214C

CDK8
N372S, V78I, splice site 1110+1G>T and splice site 205-1G>A

CHEK1
F70L

CREBBP
G211E and T872M

CRKL
A208T and F134V

CTCF
K208N

CTNNA1
K867T

CUL3
F224C and F377C

DAXX
K662N and Q469H

DIS3
E117D and R108H

DNMT3A
D702N

DOT1L
S631L

EED
L425F

EP300
E1531G, L68I and M205R

EPHA3
E647* and V626A

EPHB1
E116D, R663W and V234A

ERBB2
R1161Q

ERBB3
H578N

ERBB4
A1219T

ERG
F430C

ESR1
D218N

FAM123B
K170Q and S286N

FANCG
V64A and Y268H

FAS
R279C

FGF12
R224M and Y155D

FGF23
A213V

FGF3
R151I and S108L

FGF4
G37D

FGFR4
L113F

FH
P461T

Electronically signed by Douglas Lin, M.D. | 28 September 2021
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FLT1
F333Y and M945fs*15

FLT3
F710V

GABRA6
L424I and Y233C

GATA6
E460K and N510D

GNAS
A475V, F315C and L132M

GSK3B
A22T and R92I

HGF
L565I and P299H

HSD3B1
L167M

IDH1
R222C

IDH2
D200Y

IGF1R
E83K

IKBKE
E705K

IKZF1
K275N, S105P and S364L

INPP4B
E807D, L277V and L344R

IRS2
D276N, E1199K, P813S and S1174L

JAK1
R93C

JAK2
R803Q

KDM5A
E1098*, R893Q and R902W

KDM5C
K101N

KDM6A
R519G

KDR
E685K, G335D, R652I and V1251fs*5

KEAP1
R614Q

KEL
A311T, D497N, E352D and Y714H

KIT
R956W

KLHL6
N200H

KMT2A (MLL)
I3660V, L950I, S941Y and T3574M

LTK
K827T and S830N

MAF
N365K

MAP2K4
R304Q

MAP3K1
R532Q

MED12
L1300M, R422W, R438C and R470H

MERTK
D579Y and P81S

MET
R1166*

MITF
splice site 760-2A>C

MLH1
D63Y

MLL2
A781T, E1588K and L3776R

MSH6
A780T, E995K, K431T and R1242H

MST1R
F574L and G356D

MTOR
Q2223R

NBN
E474D

NF1
K63N, L2639I and W837L

NF2
R187I and R418C

NKX2-1
D356G

NOTCH1
A105T, D464N and G2333D

NRAS
Y4C

NSD3 (WHSC1L1)
G748V

NT5C2
K244E and K45N

NTRK1
M566T

NTRK2
E70K and R124*

NTRK3
E559G, P725H and R721C

P2RY8
S58L

PALB2
K279N

PARP1
A194V

PARP2
E222Q

PBRM1
R876C

PDCD1 (PD-1)
A50T

PDGFRA
E556*, M1073V, R346S and splice site 1122-1G>T

PDK1
K73N and R341I

PIK3CA
L285V, R230* and splice site 352+1G>A

PIK3CB
A655V, E225*, N377H and R955*

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POLD1
R177C

POLE
L1235I

PPP2R2A
E338A

PTCH1
L223I

PTEN
E157D and I5T

PTPN11
K590T

PTPRO
L832R

RAD51
L274I

RAD51B
L321R

RAD51C
S163R

RAD52
R55H

RAF1
E104K

RBM10
E705D

REL
R45Q

RET
R474W

RICTOR
H1453R, K1155T, L612R, L804I, R1110C and R222Q

ROS1
E402D, E908*, I883L, K1533N, N399H, R1212C, R922I and V785M

SETD2
P190L

SF3B1
E809* and R451Q

SGK1
L363I

SMAD2
S276L and S464A

SPEN
R535Q

SPOP
R284C

STAG2
D153N and F1214L

STAT3
T494fs*55

TBX3
A418T, E720K, R304W and S363L

TEK
splice site 3063-1G>A

TET2
A241V and Y1935H

TNFAIP3
H289Q

TSC1
K475Q, L930P and R228Q

TSC2
D8Y and K69N

U2AF1
R234C

VEGFA
P363S and S186Y

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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 994x

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