FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Sun, I Li	Prostate acinar adenocarcinoma	04 Jun 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1637928-01

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 Prostate acinar adenocarcinoma
NAME Sun, I Li
DATE OF BIRTH 03 October 1949
SEX Male
MEDICAL RECORD # 44360125

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

SPECIMEN
SPECIMEN SITE Prostate
SPECIMEN ID S112-01461 E (PF23064)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 11 January 2023
SPECIMEN RECEIVED 25 May 2023

Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - 350 Muts/Mb

Genomic Findings

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

BARD1 R406*
BRCA2 D946fs*14
BRIP1 splice site 918+1G>A - subclonal†
CDK12 R1048*, N474fs*8 - subclonal†
CHEK1 T226fs*14
FANCL G119*
EGFR G724S
APC R876*
PIK3CA E970K
PTEN P246L, K267fs*9, R173C
RNF43 G659fs*41, H683fs*17
TSC2 R57H
ASXL1 G646fs*12
ATR F222fs*11
CASP8 R250Q, Q308*
CBL splice site 1007+2T>C
CD79A V69I - subclonal†
CDK8 Q331H - subclonal†
CTCF T204fs*26
CTNNA1 K695fs*27
EPHB4 V420I
ERRFI1 F411fs*41
FH splice site 1237-1G>A
FUBP1 I301fs*4
IRF2 N167fs*7
KMT2D (MLL2) A221fs*40
MAPK1 R191H
MLH1 R127I
MSH2 loss
MSH3 N385fs*19
MSH6 loss
NOTCH3 G463*
NTRK2 A11V
PMS2 Y268fs*39
PRKAR1A Q275*
QKI K134fs*14, R124*
SETD2 R1407fs*5
SMAD4 G386S - subclonal†
SPEN K1999fs*23
TGFBR2 R497* - subclonal†
TP53 R196*, Y205H - subclonal, R175C†
XRCC2 L117fs*17

8 Disease relevant genes with no reportable alterations: ***ATM, BRCA1, CHEK2, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 33), **Pembrolizumab** (p. 35), **Rucaparib** (p. 36)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA2*** **D946fs*14** (p. 8), ***CDK12*** **N474fs*8, R1048*** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 45)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***BRCA2*** **D946fs*14** (p. 8), ***PTEN*** **K267fs*9, P246L, R173C** (p. 14), ***TP53*** **R175C, R196*, Y205H** (p. 30)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA2*** **D946fs*14** (p. 8), ***MLH1*** **R127I** (p. 23), ***PMS2*** **Y268fs*39** (p. 26)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***ASXL1*** **G646fs*12** (p. 16), ***KMT2D (MLL2)*** **A221fs*40** (p. 22)

Electronically signed by Brennan Decker, M.D., Ph.D. | 04 June 2023
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PATHOLOGIST COMMENTS

Brennan Decker, M.D., Ph.D. 04-Jun-2023

The very high TMB in this case is likely attributable to the observed microsatellite instability - high (MSI-H) phenotype. In the setting of MSI-H associated hypermutation, co-occurring mutations are often subclonal passengers resulting from the large number of mutations, rather than acting as traditional drivers. This may impact potential for therapy response (e.g., for the homologous recombination pathway alterations and PARPi, in this case; PMID: 35772050). High TMB resulting from MSI-H has been associated with response to immunotherapy. Please see the Professional Services section below for additional information.

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Pembrolizumab 2A	Atezolizumab
	Dostarlimab	Avelumab
		Cemiplimab
		Durvalumab
		Durvalumab + Tremelimumab
		Nivolumab
		Nivolumab + Ipilimumab
10 Trials see p. 45		Retifanlimab
Tumor Mutational Burden - 350 Muts/Mb	Pembrolizumab 2A	Atezolizumab
	Dostarlimab	Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
		Nivolumab + Ipilimumab
10 Trials see p. 47		Retifanlimab
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***BARD1* -** R406*	Olaparib 1	Niraparib
10 Trials see p. 50	Rucaparib	Talazoparib
***BRCA2* -** D946fs*14	Olaparib 1	Niraparib
	Rucaparib 2A	Talazoparib
10 Trials see p. 52	Olaparib + Abiraterone	

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)
BRIP1 - splice site 918+1G>A - subclonal	Olaparib [1]	Niraparib
	Rucaparib	Talazoparib
10 Trials see p. 54		
CDK12 - R1048*, N474fs*8 - subclonal	Olaparib [1]	Cemiplimab
	Dostarlimab	Niraparib
	Pembrolizumab	Nivolumab
	Rucaparib	Retifanlimab
		Talazoparib
10 Trials see p. 56		
CHEK1 - T226fs*14	Olaparib [1]	Niraparib
	Rucaparib	Talazoparib
10 Trials see p. 58		
FANCL - G119*	Olaparib [1]	Niraparib
	Rucaparib	Talazoparib
10 Trials see p. 61		
EGFR - G724S	none	Erlotinib
		Gefitinib
5 Trials see p. 60		
APC - R876*	none	none
2 Trials see p. 49		
PIK3CA - E970K	none	none
10 Trials see p. 63		
PTEN - P246L, K267fs*9, R173C	none	none
10 Trials see p. 65		
RNF43 - G659fs*41, H683fs*17	none	none
2 Trials see p. 67		
TSC2 - R57H	none	none
10 Trials see p. 68		

[ ] *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.

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.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

BIOMARKER

Microsatellite status

RESULT
MSI-High

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI has been reported in 3.1-14.6% of prostate cancer samples[12-16]. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases[17-19]. For patients with advanced prostate cancer, dMMR/MSI status was associated with shorter median OS compared with patients with proficient MMR (3.8 vs. 7.0 years) by univariate and multivariate analysis (adjusted HR=4.09; P=0.005)[20].

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[21]. 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[21-23]. This sample has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in >30% of microsatellite markers[24-26]. MSI-H status indicates high-level deficiency in MMR and typically correlates with loss of expression of at least one, and often two, MMR family proteins[21,23,25-26].

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[21], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[27]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[27-29] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[30-32]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
350 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[33-35], anti-PD-1 therapies[33-36], and combination nivolumab and ipilimumab[37-42]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[33-36,43-47]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[43]; similar findings were observed in the KEYNOTE 028 and 012 trials[36]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[47]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[48]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[46]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[49] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[34]. The Phase 2 CheckMate 650 trial of nivolumab and ipilimumab treatment for patients with metastatic castration-resistant prostate cancer reported that patients harboring above the median study TMB experienced increased ORR and PSA responses[42]. A real-world study for patients with pretreated metastatic castration-resistant prostate cancer (mCRPC) reported longer time to next therapy (TTNT) for patients with high tumor mutational burden (TMB; ≥10 Muts/Mb) treated with immune checkpoint inhibitors (ICIs) compared with those treated with taxane chemotherapies, whereas for patients with low TMB (<10 Muts/Mb), treatment with ICIs resulted in worse TTNT compared with taxanes[50].

FREQUENCY & PROGNOSIS

Prostate acinar adenocarcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 3.4% of cases have high TMB (>20 muts/Mb)[51]. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors[52-53], with approximately 0.5-1.5 (muts/Mb) in localized tumor samples[54-56], and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples[57-59]. One study reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 muts/Mb), which was due to defects in mismatch repair genes MLH1 and MSH2 in 3 of the 4 cases[59]. Published data investigating the prognostic implications of tumor mutational burden in prostate cancer are limited (PubMed, Feb 2023).

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[60-61] and cigarette smoke in lung cancer[8,62], treatment with temozolomide-based chemotherapy in glioma[63-64], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[65-69], and microsatellite instability (MSI)[65,68-69]. 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[34-36,43].

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GENE
BARD1

ALTERATION
R406*

HGVS VARIANT
NM_000465.2:c.1216C>T (p.R406*)

VARIANT CHROMOSOMAL POSITION
chr2:215645382

VARIANT ALLELE FREQUENCY (% VAF)
40.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical benefit from rucaparib has been observed in a patient with BARD1-mutated ovarian cancer[70]. On the basis of preclinical evidence, tumors with BARD1 inactivation may be sensitive to PARP inhibitors[71-74].

FREQUENCY & PROGNOSIS

BARD1 mutations have been reported in 0-2% of prostate adenocarcinoma samples[54-55,57,75]. Published data investigating the prognostic implications of BARD1 alterations in prostate carcinoma are limited (PubMed, Mar 2023).

FINDING SUMMARY

BARD1 encodes the BRCA1-associated RING domain 1 protein, which is required for stabilization and nuclear localization of BRCA1 as well as formation of the E3 ubiquitin ligase[76]. The BARD1 ANK repeats and BRCT motifs play important roles in chromosome stability, and both these regions and the RING domain are necessary for homology-directed repair[71,77-78]. Alterations such as seen here may disrupt BARD1 function or expression.

GENE
BRCA2

ALTERATION
D946fs*14

HGVS VARIANT
NM_000059.3:c.2835del (p.D946Ifs*14)

VARIANT CHROMOSOMAL POSITION
chr13:32911321-32911322

VARIANT ALLELE FREQUENCY (% VAF)
37.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[79-96] or ATR inhibitors[97-99]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[80,85,88,95-96] and for patients with platinum-resistant or -refractory disease[79,84,91,94]. 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[100]. 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[101]. 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[99]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[102], ovarian carcinoma[103], and triple-negative breast cancer (TNBC)[104] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (CRPC) who had progressed on a new hormonal agent reported improved radiographic PFS with olaparib compared with physician's choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations (7.4 vs. 3.6 mo., HR=0.34)[105]. The Phase 1/2 PETRA study of PARP1 inhibitor AZD5305 observed a 25% (10/40) ORR (10 PR), for patients with BRCA1/2, PALB2, or RAD51C-mutated breast, ovarian, pancreatic, or prostate cancer, including 5 patients with prior PARP inhibitor treatment[106].

— Nontargeted Approaches —

Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12 have been reported to be predictive for sensitivity to platinum agents in castration resistant prostate cancer (CRPC) (NCCN Prostate Cancer Guidelines, v1.2023)[107-110]. Clinical data from small retrospective studies[111] and case reports[112-116] are conflicting as to whether alterations in DNA repair genes such as BRCA1, BRCA2, and ATM are associated with outcomes for patients with CRPC treated with PSMA-targeted radionuclide-based therapies such as lutetium Lu 177 vipivotide tetraxetan (177Lu-PSMA-617). Germline BRCA2 mutations in mCRPC were associated with relative benefit from first-line abiraterone or enzalutamide compared with taxanes (CSS 24.0 vs. 17.0 months, PFS on the second systemic therapy 18.9 vs. 8.6 months) in a large prospective cohort study[117]. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy[107,118]. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[119-129].

FREQUENCY & PROGNOSIS

BRCA2 mutations have been identified in 3–6% of primary and 6–7% of metastatic prostate cancer specimens[56,59,130], with deleterious germline BRCA2 mutations present for 5% of patients with metastatic prostate cancer[131]. BRCA2 homozygous deletion has been reported in 3–6% of prostate adenocarcinoma cases[75,132-133]. The positive predictive value of prostate specific antigen (PSA) levels was found to be higher in patients with BRCA1/2 mutations than in the general population[134]. BRCA2 germline mutations predict poor prognosis for patients with prostate cancer (NCCN Prostate Cancer Guidelines, v1.2023)[135-141] and have been associated with attributes of aggressive prostate cancer at diagnosis, including high Gleason score, nodal involvement, advanced tumor stage, and metastatic spread[135]. An exome sequencing study of aggressive and non-aggressive prostate cancer cases reported that patients with pathogenic, likely pathogenic, or deleterious BRCA2 mutations had statistically higher odds of aggressive disease (4.3-fold), prostate cancer death (4.7-fold), and metastatic disease (5.7-fold)[142]. In another study, germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers[135]. Following radical conventional treatment for localized prostate cancer, patients with germline BRCA1/2 mutations experienced significantly shorter metastasis-free survival (HR=2.36) and CSS (HR=2.17) than noncarriers[143]. Patients with germline or somatic BRCA2 mutations have been reported to experience significantly shorter time to castration-resistant disease progression on first-line abiraterone or enzalutamide treatment (9.4 vs. 18.4 months, HR=1.58) and significantly shorter OS (16.9 vs. 21.8 months, HR=1.64)[144]. For patients with metastatic castration-resistant prostate cancer (mCRPC), germline BRCA2 mutations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in 1 study[117].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[145]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[146]. Alterations such as seen here may disrupt BRCA2 function or expression[145,147-162].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA2 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 breast and ovarian cancer syndrome (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[164-165], 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[166]. 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%[167]. 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[166,168-173]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

GENE

BRIP1

ALTERATION
splice site 918+1G>A - subclonal

HGVS VARIANT
NM_032043.2:c.918+1G>A (p.?)

VARIANT CHROMOSOMAL POSITION
chr17:59885827

VARIANT ALLELE FREQUENCY (% VAF)
6.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical responses in ovarian cancer[85] and prostate cancer[174], as well as clinical benefit in breast cancer[175], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors.

FREQUENCY & PROGNOSIS

BRIP1 mutation has been reported in <1% of prostate cancer samples (cBioPortal, Apr 2023)[176-177]. Published data investigating the prognostic implications of BRIP1 alterations in prostate cancer are limited (PubMed, Aug 2022).

FINDING SUMMARY

BRIP1, also known as FANCJ (Fanconi Anemia complementation group J) and BACH1, encodes a DNA helicase required for DNA repair and the maintenance of chromosomal stability[178-180]. Alterations such as seen here may disrupt BRIP1 function or expression[178,181-183].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRIP1 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 breast cancer (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in BRIP1 are associated with increased risk of breast, ovarian, and cervical cancers[184-188]. Germline mutations in BRIP1 are also associated with Fanconi anemia (FA), a rare autosomal disorder that predisposes patients to a subset of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), gynecological malignancies, and head and neck tumors[189-191]; frequency estimates suggest an incidence of 3/1,000,000 individuals in Europe and the US, and a heterozygote carrier frequency of 1/181 to 1/300 in the US and Europe, respectively, with slightly higher rates in some populations, such as the Ashkenazi Jewish population (1/89)[190,192]. In the appropriate clinical context, germline testing of BRIP1 is recommended.

GENE

CDK12

ALTERATION
R1048*, N474fs*8 - subclonal

HGVS VARIANT
NM_016507.2:c.3142C>T (p.R1048*),
NM_016507.2:c.1421del (p.N474Ifs*8)

VARIANT CHROMOSOMAL POSITION
chr17:37680973, chr17:37627500-37627501

VARIANT ALLELE FREQUENCY (% VAF)
38.9%, 7.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK12 inactivation in cancer is associated with genomic instability characterized by tandem duplications[193-197] and has been shown to increase tumor immunogenicity in advanced prostate cancer[194]. On the basis of clinical and preclinical evidence in prostate cancer, CDK12 inactivation may predict benefit from immune checkpoint inhibitors[194,198-199]. Retrospective studies observed prostate-specific antigen (PSA) response rates of 11-50% (2/19-2/4) for patients with CDK12-mutated metastatic prostate cancer on immune checkpoint inhibitors (predominantly anti-PD-1 monotherapy)[194,198-200]. The prospective NEPTUNES trial of nivolumab plus ipilimumab reported a composite response rate of 14% (1/7) in CDK12-mutated metastatic castration-resistant prostate cancer (mCRPC), with the responder also having high tumor-infiltrating lymphocytes[201]. In a similar treatment population, the prospective IMPACT trial for patients with CDK12-inactivated mCRPC reported PSA ≥50% decline in 14% (4/28) of patients and unconfirmed PSA ≥30% decline in 21% (6/28) of patients following treatment with nivolumab plus ipilimumab[202]. Preclinical data suggest CDK12 inactivating alterations may sensitize cells to PARP inhibitors[203-208], and the Phase 3 PROfound study reported numerically improved PFS for patients with CDK12-altered tumors treated with olaparib compared to control androgen deprivation therapy (5.1 vs. 2.2 months)[209]. However, multiple clinical studies have observed no radiographic responses for patients with CDK12-altered CRPC treated with PARP inhibitors[174,210].

— Nontargeted Approaches —

Cells lacking CDK12 incur spontaneous DNA damage and exhibit heightened sensitivity to DNA-damaging agents[203-208]. Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12 have been reported to be predictive for sensitivity to platinum agents in castration resistant prostate cancer (CRPC) (NCCN Prostate Cancer Guidelines, v1.2023)[107-110]. Studies on the impact of CDK12 alterations on response to taxanes for patients with metastatic castration-resistant prostate cancer (mCRPC) are conflicting (NCCN Prostate Cancer Guidelines, v1.2023)[198,211].

FREQUENCY & PROGNOSIS

CDK12 mutation has been reported in 4.3-6.9% of patients with metastatic castration-resistant prostate cancer (mCRPC)[194,212-214]. The frequency of CDK12 mutations has been reported to be higher in mCRPC than in primary prostate cancer, where CDK12 mutations have been observed in 1.2% of patients[194]. Retrospective analyses of prostate cancer have found that CDK12 alterations are associated with high-risk features, including high Gleason scores and de novo metastases, with most patients developing CRPC[200,212,214]. Retrospective analyses of prostate cancer found that among patients presenting with localized disease, CDK12 mutation was associated with shorter time to metastasis (34.9 vs. 55.6-64.7 months, HR=0.46-0.59) and earlier development of CRPC (32.7 vs. 56.2-72.8 months, HR=0.42-0.51) compared with the non-CDK12 study cohorts[200]; another retrospective analysis reported that patients with CDK12 alterations experienced earlier development of CRPC prostate-specific antigen PFS on first-line abiraterone or enzalutamide treatment[144]. Additional studies report that CDK12 alteration or biallelic loss is associated with shorter OS (64.4 vs. 74.9 months, HR=1.70 and 61.2 vs. 76.8 months, HR=1.65, respectively)[212,214]. A study of 59 patients with hormone-sensitive prostate cancer identified MSH2, CDK12, RB1, and TP53 alterations as independent risk factors for early progression to castration-resistant prostate cancer[215].

FINDING SUMMARY

CDK12 encodes a cyclin-dependent kinase that interacts with cyclin K to regulate the phosphorylation of RNA polymerase II and the expression of genes involved in maintaining genomic stability, including BRCA1 and ATR[216]. Alterations such as seen here may disrupt CDK12 function or expression[206,217-219].

GENE
CHEK1

ALTERATION
T226fs*14

HGVS VARIANT
NM_001274.4:c.676del (p.T226Hfs*14)

VARIANT CHROMOSOMAL POSITION
chr11:125505377-125505378

VARIANT ALLELE FREQUENCY (% VAF)
41.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In preclinical studies, loss of CHEK1 activity has been shown to sensitize cancer cells to DNA-damaging agents, including PARP inhibitors[220-224]. CHEK1 inhibitors have shown clinical benefit for patients with a variety of solid and hematologic cancers, but it is not known if CHEK1 mutation confers sensitivity to these inhibitors[225-228].

FREQUENCY & PROGNOSIS

CHEK1 mutations have been generally observed at low frequencies in cancer, with greatest prevalence in non-melanoma skin cancer (2.7%), endometrial cancer (1.8%), and melanoma (1.4%)[229]. CHEK1 expression was reported to be higher in TNBC and basal-like breast cancer as compared with benign lesions and other types of malignant breast cancer[230-231]. One study found that CHEK1 was the most upregulated kinase in glioblastoma and was overexpressed in all subtypes compared with healthy cells or to low-grade glioma[232]. However, CHEK1 deletion or methylation was detected more frequently in cervical carcinoma than in premalignant cervical lesions (80% vs. 35%, respectively), and CHEK1 expression was also reduced in these cells as compared with normal cervical tissues[233]. CHEK1 alterations have been associated with reduced survival for patients with cervical cancer[233]. High CHEK1 expression or phosphorylation correlated with aggressive phenotypes and a poorer prognosis in glioma, breast cancer, hepatocellular carcinoma, and non-small cell lung cancer[232,234-236].

FINDING SUMMARY

CHEK1 encodes CHK1, a serine/threonine protein kinase that is required for checkpoint-mediated cell cycle arrest in response to DNA damage and maintains genome integrity by activating homologous recombination repair[223,237-240]. In more than half of cancers, the ATM/CHK2/p53 pathway is compromised, and the ATR/CHK1/CDC25 pathway provides cell-cycle arrest needed for repair of DNA damage[238]. Alterations such as seen here may disrupt CHEK1 function or expression[241-244].

GENE
FANCL

ALTERATION
G119*

HGVS VARIANT
NM_018062.3:c.355G>T (p.G119*)

VARIANT CHROMOSOMAL POSITION
chr2:58449096

VARIANT ALLELE FREQUENCY (% VAF)
40.4%

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[70,245] .

FREQUENCY & PROGNOSIS

FANCL mutations are most frequently observed in tumors of the prostate (5.3%) and liver (4.0%), and are seen at lower frequency in other tumor types (COSMIC, May 2023)[246]. Published data investigating the prognostic implications of FANCL alterations in solid tumors and hematologic malignancies are limited (PubMed, May 2023). 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[247].

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[248]. 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[249]. Alterations such as seen here may disrupt FANCL function or expression[250-257]. 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[191,258-261].

GENE
EGFR

ALTERATION
G724S

HGVS VARIANT
NM_005228.3:c.2170G>A (p.G724S)

VARIANT CHROMOSOMAL POSITION
chr7:55241722

VARIANT ALLELE FREQUENCY (% VAF)
37.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR-TKIs, including erlotinib[262], gefitinib[263-266], afatinib[267-270], dacomitinib[271], and osimertinib[268,272]; however, the data for patients with other tumor types are limited[273-278].

— Potential Resistance —

EGFR G724S mediates resistance to osimertinib; notably, virtually all reported evidence for clinical and preclinical resistance of G724S to this agent has been in the context of co-occurrence with activating exon 19 deletions[279-285] irrespective of the presence of T790M[279-283,286]. G724S co-occurring with other activating alterations is rare[285], and, therefore, it is unclear whether EGFR G724S would reduce sensitivity to osimertinib outside of EGFR exon 19 deletions. G724S also reduces resistance to first-generation EGFR inhibitors, with a retrospective analysis reporting emergence of G724S in 4 patients with non-small cell lung cancer (NSCLC) who progressed on erlotinib or gefitinib; 3 harbored concurrent activating exon 19 deletions and 1 harbored a concurrent L861G activating mutation[287]. However, in other studies, 2 additional patients, 1 with concurrent S768I activating mutation, experienced SD to these inhibitors[288-289].

FREQUENCY & PROGNOSIS

EGFR mutation and amplification have been observed in 6.6% and 0.7-4.1% of prostate carcinoma cases, respectively (cBioPortal, COSMIC, Dec 2022)[176-177,246]. Many studies have reported EGFR overexpression in prostate cancer, cited in 25-42% of cases[290-294]. One study reports no significant correlation between EGFR expression and PSA levels[293]. Higher levels of EGFR have been correlated with poor prognosis and higher Gleason score in prostate cancer patients[291,293].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[295]. The G724S mutation seen here has been characterized as activating[296] and confers resistance to first-generation EGFR inhibitors in the context of co-occurring activating EGFR alterations[287,297-300]. In the context of co-occurring EGFR exon 19 deletions, G724S has demonstrated resistance to osimertinib[279-283,286]. Limited preclinical evidence for resistance to erlotinib[285], gefitinib[281], and osimertinib[281] has also been reported for G724S alone.

GENE
APC

ALTERATION
R876*

HGVS VARIANT
NM_000038.4:c.2626C>T (p.R876*)

VARIANT CHROMOSOMAL POSITION
chr5:112173917

VARIANT ALLELE FREQUENCY (% VAF)
39.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[301], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[302-303]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[304]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[305-306].

FREQUENCY & PROGNOSIS

APC mutations and homozygous deletions were observed in 0.6%-6.7% and 0.6%-4.5% of prostate adenocarcinoma cases, respectively[56,59,132,307]. APC methylation has been frequently observed in prostate carcinoma[308-310], and dysregulation of the WNT signaling pathway is believed to play a role in a subset of prostate cancers[311-312]. In prostate cancer, APC promoter hypermethylation is associated with shorter time to relapse in both univariate (P = 0.002) and multivariate analyses[313]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[314].

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[315]. Alterations such as seen here may disrupt APC function or expression[316-320].

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, Apr 2023)[163]. 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)[321-323]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[324], and in the appropriate clinical context germline testing of APC is recommended.

GENE
PIK3CA

ALTERATION
E970K

HGVS VARIANT
NM_006218.2:c.2908G>A (p.E970K)

VARIANT CHROMOSOMAL POSITION
chr3:178948136

VARIANT ALLELE FREQUENCY (% VAF)
41.5%

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[325-332], AKT[333-334], or mTOR[335-342]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[332]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[331]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[329-330]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[343]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[344]. 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)[345]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[346], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[326].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in up to 4.3% of prostate adenocarcinomas[54,56,75,347]. PI3K pathway dysregulation in prostate cancer has been reported in numerous studies, noting either PIK3CA mutation, amplification, or overexpression, or PTEN deletion[348-350]. Retrospective analysis of the Prostate Adenocarcinoma TCGA dataset showed a significant association between PIK3CA alteration, including amplification, with decreased survival (HR=0.55), increased regional lymph node metastasis, higher primary tumor category, and higher Gleason grade[351].

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[352-353]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[354-375].

GENE
PTEN

ALTERATION
P246L, K267fs*9, R173C

HGVS VARIANT
NM_000314.4:c.737C>T (p.P246L),
NM_000314.4:c.800del (p.K267Rfs*9),
NM_000314.4:c.517C>T (p.R173C)

VARIANT CHROMOSOMAL POSITION
chr10:89717712, chr10:89717769-89717770, chr10:89711899

VARIANT ALLELE FREQUENCY (% VAF)
43.4%, 36.6%, 39.3%

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[330,376-378]. The Phase 3 IPATential150 trial combining either ipatasertib or placebo with abiraterone and prednisolone for patients with no prior treatment for metastatic castration-resistant prostate cancer (CRPC) reported superior radiographic PFS (18.5 vs. 16.5 months, HR=0.77) and ORR (61% vs. 39%) with ipatasertib for patients with PTEN loss as determined by immunohistochemistry[379]. A Phase 2 study combining either ipatasertib or placebo with abiraterone and prednisolone for metastatic CRPC reported improved radiographic PFS from the addition of ipatasertib for patients with PTEN loss (11.5 vs. 4.6 months, HR=0.39), but limited benefit for those without PTEN loss (7.5 vs. 5.6 months, HR=0.84)[380]. A Phase 2 trial combining either the AKT inhibitor capivasertib or placebo with docetaxel and prednisolone for patients with metastatic CRPC reported prolonged OS (31.2 vs. 20.3 months, HR=0.54) with the addition of capivasertib but comparable composite PFS (7.0 vs. 6.7 months, HR= 0.92) between trial arms; OS and PFS were consistent irrespective of PTEN, PI3K, or AKT status[381]. Multiple studies of mTOR inhibitors including everolimus and temsirolimus have been terminated due to limited efficacy, reporting brief PFS (1.9-3.6 months)[382-386]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[387-391], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[392], ovarian cancer[245], uterine leiomyosarcoma[393], and endometrial cancer[391] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[84,394].

— Nontargeted Approaches —

In post-hoc analyses of a Phase 1/2 trial, the addition of carboplatin to cabazitaxel significantly improved PFS (6.0 vs. 2.2 months) and OS (17.4 vs. 9.9 months) for patients with an aggressive variant prostate cancer molecular signature (AVPC-MS, composed of alterations in at least 2 of the genes RB1, TP53, and PTEN); no significant difference in outcomes were observed for patients lacking this signature (NCCN Prostate Cancer Guidelines, v1.2023)[395]. Post-hoc analysis of a Phase 2 trial in metastatic castration-resistant prostate cancer suggests that patients with aggressive variant prostate cancer (AVPC), molecularly characterized by harboring alterations in at least 2 genes of TP53, RB1, and PTEN, as seen in this sample, may benefit from cabazitaxel combined with carboplatin compared with cabazitaxel alone (median PFS of 5.1 vs. 2.2 months, p=0.03; estimated median OS of 11.2 vs. 10.5 months, p=0.11), whereas patients who were AVPC-negative did not benefit from the more intense chemotherapy combination in this study[395].

FREQUENCY & PROGNOSIS

PTEN mutations have been reported in up to 10% of prostate carcinoma cases[56,59,133,347], while PTEN loss been reported in 15-36% of cases[56,59,133]. Reduction or loss of PTEN protein expression has been found in 18-61% of prostate cancer cases and has been found to be associated with more advanced stage, more rapid progression to metastasis, and reduced patient survival[396-400]. Concurrent alterations in at least 2 of the TP53, RB1, and PTEN genes, as seen in this sample, molecularly define a subtype of prostate cancer with aggressive clinical course and reduced sensitivity to androgen-deprivation therapies (NCCN Prostate Cancer Guidelines, v1.2023)[395,401-404].

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[377]. Alterations such as seen here may disrupt PTEN function or expression[405-446].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hamartoma tumor syndrome (ClinVar, Apr 2023)[163]. 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[447-448]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[447,449]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[447]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
RNF43

ALTERATION
G659fs*41, H683fs*17

HGVS VARIANT
NM_017763.4:c.1976del (p.G659Vfs*41),
NM_017763.4:c.2043del (p.H683Ifs*17)

VARIANT CHROMOSOMAL POSITION
chr17:56435160-56435161, chr17:56435093-56435094

VARIANT ALLELE FREQUENCY (% VAF)
37.9%, 41.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

RNF43 alterations may lead to WNT activation and therefore may confer sensitivity to WNT pathway inhibitors such as porcupine (PORCN) inhibitors[450-454], but this has not been clinically established[455]. In a Phase 1 basket study of the PORCN inhibitor RXC004, SD was reported for 1/2 patients with RNF43-mutated tumors[456]. RNF43 mutations did not clearly correlate with change in tumor baseline in a Phase 2 study of the addition of the PORCN inhibitor WNT974 to the combination of encorafenib and cetuximab to treat patients with BRAF V600E-mutated metastatic colorectal cancer (CRC)[455]. A meta-analysis of patients with BRAF V600E-mutated CRC suggests that RNF43 mutations may predict improved clinical benefit from BRAF/EGFR combinatorial therapies in the context of microsatellite-stable disease[457].

FREQUENCY & PROGNOSIS

RNF43 alterations have been reported predominantly in endometrial (18-27%)[458-459] and gastrointestinal cancers such as colorectal cancer (CRC; 19%)[68,459-460] and gastric cancer (11-18%)[461-462], where they are associated with MMR deficiency and microsatellite instability (MSI)[457,459-463]. One study found that patients with Stage 4 RNF43-mutated right-sided CRC had significantly worse OS than patients with RNF43-wildtype right-sided or RNF43-mutated left-sided CRC[464]. Co-occurrence of RNF43 and KRAS activating mutations are associated with numerically poorer outcomes in CRC[465].

FINDING SUMMARY

RNF43 is a tumor suppressor and encodes a ubiquitin ligase that functions as a negative regulator of WNT signaling[450-454,465-466].

GENE
TSC2

ALTERATION
R57H

HGVS VARIANT
NM_000548.3:c.170G>A (p.R57H)

VARIANT CHROMOSOMAL POSITION
chr16:2100432

VARIANT ALLELE FREQUENCY (% VAF)
43.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC2 can activate mTOR signaling[467]. MTOR inhibitors such as everolimus, temsirolimus, and sirolimus have shown activity against tumors associated with the genetic disease tuberous sclerosis complex (TSC), including subependymal giant cell astrocytomas and renal angiomyolipomas[468-473]. Sirolimus and nab-sirolimus have shown activity for patients with TSC2-altered malignant perivascular epithelioid cell tumors[474-476]. Nab-sirolimus has also shown limited activity for patients with TSC2-mutated sarcomas as a monotherapy[477] or in combination with nivolumab[478]. In the context of TSC2-altered malignancies unrelated to TSC, everolimus and temsirolimus activity has been limited[479-481] with the exception of anecdotal reports across various solid tumors, including anaplastic thyroid cancer[482], renal cell carcinoma (RCC)[483-484], glioblastoma (GBM)[485], and central nervous system embryonal tumor[486], as well as a case of Hodgkin lymphoma[487]. In the prospective NCI-MATCH study, only 6.7% (1/15) of patients with TSC2-mutated solid tumors responded to everolimus, with the single response reported for 1 patient with uterine leiomyosarcoma[479]. 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[488].

FREQUENCY & PROGNOSIS

TSC2 mutation and loss have been reported in up to 1.8% and 4.2%, respectively, of prostate carcinoma samples analyzed in large datasets[132,214,489-490]. Published data investigating the prognostic implications of TSC2 alterations in prostate carcinoma are limited (PubMed, Feb 2023).

FINDING SUMMARY

The tumor suppressor protein Tuberin (TSC2) binds with Hamartin (TSC1) to inhibit mTOR signaling and cell growth[467,491]. Alterations such as seen here may disrupt TSC2 function or expression[492-494].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC2 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 (RCC)[495-497]. TSC2 mutations account for approximately 75 to 80% of reported sporadic cases[498]. 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[498]. In the appropriate clinical context, germline testing of TSC2 is recommended.

GENE
ASXL1

ALTERATION
G646fs*12

HGVS VARIANT
NM_015338.5:c.1934dup (p.G646Wfs*12)

VARIANT CHROMOSOMAL POSITION
chr20:31022441

VARIANT ALLELE FREQUENCY (% VAF)
35.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

ASXL1 alterations occur infrequently across various solid tumor types[229] and are not known to act as drivers in any specific solid cancer type[499]. Published data investigating the prognostic implications of ASXL1 alterations in solid tumors are limited (PubMed, May 2023). In the context of clonal hematopoiesis, ASXL1 mutations are significantly enriched in current or former smokers[500].

FINDING SUMMARY

ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors[501-503]. Alterations such as seen here may disrupt ASXL1 function or expression[504-506].

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[507-512]. 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[507-508]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[513]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[511,514-515]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
ATR

ALTERATION
F222fs*11

HGVS VARIANT
NM_001184.3:c.666del (p.F222Lfs*11)

VARIANT CHROMOSOMAL POSITION
chr3:142281577-142281578

VARIANT ALLELE FREQUENCY (% VAF)
36.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 2 study reported talazoparib led to a SD lasting over 6 months for a patient with ATR-mutated breast cancer[516]. Based on preclinical evidence, ATR-deficient tumors may be sensitive to PARP inhibitors[224,517].

FREQUENCY & PROGNOSIS

ATR mutations or loss have been reported in <1% of prostate adenocarcinomas in multiple studies[54-57,59,133]. ATR inactivation, either by mutation or decreased expression, is associated with increased microsatellite instability (MSI) and chromosome instability (CIN) in a variety of tumor types, including colorectal and endometrial cancers[518-520]. Published data investigating the prognostic implications of ATR alterations in prostate carcinoma are limited (PubMed, Oct 2022). Other alterations leading to defective DNA repair have been reported in 23-33% of metastatic castration-resistant prostate cancer cases, and mutations in DNA repair-associated genes have been associated with response to the PARP inhibitor olaparib for patients with prostate cancer[59,80]; however, alterations in ATR have not been associated with outcomes in these studies.

FINDING SUMMARY

ATR encodes the protein ataxia telangiectasia and RAD3 related, which phosphorylates the tumor suppressor BRCA1, and several cell cycle checkpoint proteins including CHK1; it plays a key role in maintaining genome integrity via regulation of DNA repair and replication[521-522]. Alterations such as seen here may disrupt ATR function or expression[523].

GENE
CASP8

ALTERATION
R250Q, Q308*

HGVS VARIANT
NM_001228.4:c.749G>A (p.R250Q),
NM_001228.4:c.922C>T (p.Q308*)

VARIANT CHROMOSOMAL POSITION
chr2:202141587, chr2:202149607

VARIANT ALLELE FREQUENCY (% VAF)
42.2%, 43.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted approaches to directly address alterations in CASP8.

FREQUENCY & PROGNOSIS

CASP8 mutations have been observed across solid tumors[229], including 8.2% of head and neck squamous cell[524], 3.2% of colorectal[525], and 4% of cervical[526] carcinoma cases. Reduced expression of CASP8 has been associated with poor prognosis in ovarian cancer[527], prostate cancer[528], and medulloblastoma[529].

FINDING SUMMARY

CASP8 encodes caspase-8, a multifunctional protein that mediates apoptosis[530-533], cell motility[534-535], and cell signaling, including through the NFkB[536-538] and MAPK[539-540] pathways. The role of CASP8 in cancer is complex and context-dependent, with diverse cancer types exhibiting either overexpression or loss of expression. CASP8 mutations found in the context of cancer tend to be truncating or missense mutations; most of the characterized mutations impair apoptosis[541-545] and promote NFkB activation[546].

GENE
CBL

ALTERATION
splice site 1007+2T>C

HGVS VARIANT
NM_005188.2:c.1007+2T>C (p.?)

VARIANT CHROMOSOMAL POSITION
chr11:119146846

VARIANT ALLELE FREQUENCY (% VAF)
38.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CBL inactivation may lead to the hyperactivation of various receptor tyrosine kinases (RTKs), including MET[547], PDGFRA[548], KIT[549], VEGFR2[550], and the TAM (TYRO3, AXL, MER) RTKs[551]. These RTKs are targets of the multikinase inhibitor sitravatinib[552], which has shown activity in CBL-mutated advanced solid tumors[553]. Among 8 patients with CBL inactivating alterations in a Phase 1b trial, sitravatinib produced 2 PRs (25% ORR), with 1 NSCLC and 1 melanoma responding for over 4 months, and 4 SD outcomes, with 3 prolonged SDs seen in a patient with NSCLC, a patient with esophageal cancer, and a patient with a pancreatic neuroendocrine tumor[553]. CBL has been shown to downregulate EGFR[554-558] and FLT3[559-561]. Preclinical models of myeloid malignancies have demonstrated that CBL inactivation confers sensitivity to the FLT3-targeting therapies sunitinib[559], midostaurin[561], and quizartinib[562], as well as to dasatinib[563], although clinical evidence for this approach in solid tumors is lacking.

FREQUENCY & PROGNOSIS

CBL mutations have been reported in 2.4% of prostate adenocarcinoma samples analyzed in the COSMIC database (COSMIC, Jul 2022)[246]. Preclinical studies have shown that targeted reduction of CBL expression reduced proliferation and viability of prostate cancer cell lines and tumor growth of prostate cancer xenotransplants[564-565]. One study identified strong cytoplasmic CBL expression by immunohistochemistry in prostate cancer samples as compared with normal prostate tissue; increased levels of CBL protein were a significant independent predictor of reduced patient survival[565].

FINDING SUMMARY

CBL encodes an E3 ubiquitin protein ligase that is involved in cell signaling and ubiquitination, targeting proteins such as EGFR, FGFR1, FGFR2, PDGFR-alpha, PDGFR-beta, FLT3, and SRC for degradation by the proteasome[566-570]. CBL alterations that result in loss or disruption of the tyrosine kinase binding domain, RING finger domain, and/or tail domain, as observed here, are predicted to be inactivating and to promote tumorigenesis[571-588].

GENE
CD79A

ALTERATION
V69I - subclonal

HGVS VARIANT
NM_001783.3:c.205G>A (p.V69I)

VARIANT CHROMOSOMAL POSITION
chr19:42383185

VARIANT ALLELE FREQUENCY (% VAF)
2.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical[589] and preclinical[590-591] studies in activated B-cell (ABC)-diffuse large B-cell lymphoma (DLBCL), CD79A activating alterations may indicate sensitivity to the BTK inhibitor ibrutinib. In a Phase 1/2 study of ibrutinib for patients with relapsed or refractory DLBCL, 1 patient with a subclonal 45bp deletion affecting the CD79A ITAM domain experienced a CR[589]. Limited preclinical data in ABC-DLBCL cell lines suggest that CD79A mutation may also be associated with sensitivity to the SRC/BCR-ABL kinase inhibitor dasatinib[590] or to PKC inhibition[592]. However, these approaches have not been evaluated in the context of CD79A mutations in solid tumors. 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

CD79A mutations are rare (0-1.7%) in solid tumors and more commonly found in diffuse large B-cell lymphomas (DLBCL) (COSMIC, Dec 2022)[246,593]. Published data investigating the prognostic implications of CD79A alteration in solid tumors are limited (PubMed, Dec 2022).

FINDING SUMMARY

CD79A encodes B-cell antigen receptor complex-associated protein alpha chain, also known as CD79a or Ig-alpha, a critical component of the B-cell receptor (BCR) that forms a heterodimer with CD79b, which functions in BCR signal transduction. BCR signaling ultimately leads to the activation of several downstream signaling pathways, including NF-kappaB, PI3K, mitogen-activated protein kinase (MAPK), and RAS pathways, which promote cell proliferation and survival[594]. BCR signaling is considered an important oncogenic pathway in several types of lymphomas, and somatic mutations in CD79A and especially CD79B have been reported to occur frequently in the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) but only rarely or not at all in the other DLBCLs and types of lymphomas studied[590,594]. 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
CDK8

ALTERATION
Q331H - subclonal

HGVS VARIANT
NM_001260.1:c.993G>T (p.Q331H)

VARIANT CHROMOSOMAL POSITION
chr13:26974649

VARIANT ALLELE FREQUENCY (% VAF)
1.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in CDK8. Investigational inhibitors that selectively target CDK8 and the related CDK19 have shown activity against WNT-dependent tumors in preclinical assays[595-599].

FREQUENCY & PROGNOSIS

CDK8 amplification has been reported at low frequencies in solid tumors, including 3% of colorectal (CRC) and <1% of bladder, breast, sarcoma, and non-small cell lung cancer (NSCLC) samples[229]. In CRC, CDK8 expression is associated with reduced survival[600-601].

FINDING SUMMARY

CDK8 encodes a member of the cyclin-dependent kinase (CDK) family that regulates gene expression and cellular signaling including the WNT/beta-catenin and NOTCH pathways[595,602-603]. CDK8 acts as an oncogene in colon cancer and melanoma[604-606].

GENE
CTCF

ALTERATION
T204fs*26

HGVS VARIANT
NM_006565.3:c.610dup (p.T204Nfs*26)

VARIANT CHROMOSOMAL POSITION
chr16:67645338

VARIANT ALLELE FREQUENCY (% VAF)
40.3%

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, 2023)[176-177]; 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[607-608].

FINDING SUMMARY

CTCF encodes an 11-zinc-finger protein that is implicated in various regulatory roles, including gene activation and repression, imprinting, insulation, methylation, and X chromosome inactivation[609]. CTCF plays a role in transcriptional regulation of a number of key cancer-associated genes, including the oncogene MYC[610] and tumor suppressor TP53[611], via maintenance of local DNA methylation status. Decreased expression levels of CTCF and/or BORIS, another 11-zinc-finger transcriptional regulator, were reported to be closely associated with global DNA methylation variability and decreased OS in epithelial ovarian cancer[612-613].

GENE
CTNNA1

ALTERATION
K695fs*27

HGVS VARIANT
NM_001903.2:c.2084del (p.K695Rfs*27)

VARIANT CHROMOSOMAL POSITION
chr5:138266231-138266232

VARIANT ALLELE FREQUENCY (% VAF)
40.7%

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 (7.0%)[614], cutaneous melanoma (6.4%)[615], colorectal adenocarcinoma (4.9%)[614], and stomach adenocarcinoma (3.90%) TCGA datasets (cBioPortal, 2023)[176-177]. CTNNA1 mutations have been observed in patients with hereditary diffuse gastric carcinoma without CDH1 mutations[616-617]. Reduced CTNNA1 expression in patients with breast cancer has been correlated with a poor clinical outcome and breast cancer brain metastasis[618-619]. 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[620-622] and a trend for inferior survival[620]. 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[622-624].

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[625-626]. 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[625-626]; 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[619,627]. 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[619]. 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[628].

GENE
EPHB4

ALTERATION
V420I

HGVS VARIANT
NM_004444.4:c.1258G>A (p.V420I)

VARIANT CHROMOSOMAL POSITION
chr7:100417218

VARIANT ALLELE FREQUENCY (% VAF)
48.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[629], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[630]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[629,631-635]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[636-638].

FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[639-642], gastric and esophageal[643-647], colorectal carcinoma (CRC)[648-654], breast[655-659], ovarian[659-661], endometrial[662-664], thyroid[665-667], lung[668-669], glioma[670-671], and other solid tumors[631,672-679]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[631,639,655,660-661,669,672,674], histological grade[645,655,662,671], and hormone receptor status[658,663]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][653], HNSCC (HR = 2.95)[642], epithelial ovarian cancer (HR = 4.53)[659], or glioma (HR = 3.21)[671].

FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[680]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[681], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[682-683]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[684]. EPHB4 amplification has been reported in several solid tumor types[639-640,645,685-686] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[639]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[635].

GENE
ERRFI1

ALTERATION
F411fs*41

HGVS VARIANT
NM_018948.3:c.1233del (p.F411Lfs*41)

VARIANT CHROMOSOMAL POSITION
chr1:8073425-8073426

VARIANT ALLELE FREQUENCY (% VAF)
41.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERRFI1 loss or inactivating mutations may result in EGFR activation and predict sensitivity to ERBB tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and lapatinib, which are approved to treat lung or breast cancers. One patient with cholangiocarcinoma and an ERRFI1 loss of function mutation was reported to have a partial response to the EGFR inhibitor erlotinib[687]. In preclinical studies, the EGFR inhibitor gefitinib was reported to cause regression of tumors in ERRFI1 knockout mice[688] and inhibit signaling downstream EGFR in ERRFI1-depleted human cell lines[689].

FREQUENCY & PROGNOSIS

ERRFI1 mutation has been reported in 0-2% of metastatic prostate cancer cases[57,59]. In one study, ERRFI1 was identified as one of 87 genes with significantly altered expression levels in prostate cancer cell lines upon androgen treatment[690]. Published data investigating the prognostic implications of ERRFI1 alterations in prostate carcinoma are limited (PubMed, Nov 2022).

FINDING SUMMARY

The ERRFI1 gene (also known as MIG6 or RALT) encodes a tumor suppressor that negatively regulates the ERBB family of receptors[691-694], and is transcriptionally activated by RAS-RAF-ERK signaling[695]. ERRFI1 directly binds to the kinase domain of ERBB proteins and consequently antagonizes their oncogenic signaling and cell proliferation[691-694]. ERRFI1 also negatively regulates signaling by promoting EGFR endocytosis and degradation[696-697]. Knockout or depletion of ERRFI1 was shown to result in EGFR and ERBB2/ERBB3 activation[688,695,697-698], and disruption of the ERRFI1 gene promoted tumorigenesis in mice[688,699], whereas overexpression of ERRFI1 inhibited EGFR- or ERBB2-mediated signaling and oncogenic transformation in vitro[697,700-701]. Alterations such as seen here may disrupt ERRFI1 function or expression[691,693].

GENE
FH

ALTERATION
splice site 1237-1G>A

HGVS VARIANT
NM_000143.3:c.1237-1G>A (p.?)

VARIANT CHROMOSOMAL POSITION
chr1:241663891

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A preclinical study showed that FH-deficient renal cancer cells are dependent on ABL1 activity and sensitive to the multikinase inhibitor vandetanib; treatment with vandetanib inhibited the growth and tumorigenicity of these cells in vitro and in vivo[702]. Tumors with FH loss or inactivation may therefore be sensitive to vandetanib, which is approved to treat medullary thyroid cancer and is in clinical trials in solid tumors. A Phase 2 trial of bevacizumab and erlotinib reported overall response rate in 60% (12/20) of patients with hereditary leiomyomatosis and renal cell cancer, and 29% (6/21) of patients with sporadic papillary renal cell carcinoma[703].

FREQUENCY & PROGNOSIS

FH mutations are rare in solid and hematologic malignancies[229]. FH-deficient renal cell carcinoma (RCC) arises in about 20% of families affected by hereditary leiomyomatosis and renal cell cancer (HLRCC) and is associated with aggressive disease and poor prognosis[704-706].

FINDING SUMMARY

FH encodes fumarate hydratase, an enzymatic component of the Krebs cycle. FH has been identified as a possible hypoxia inducible factor activating gene[707]. Loss-of-function germline mutations in FH are associated with hereditary leiomyomatosis and renal cell cancer (HLRCC); tumors arising in FH mutation carriers often demonstrate FH biallelic inactivation[704,706,708-709].

POTENTIAL GERMLINE IMPLICATIONS

FH germline inactivating alterations are associated with FH tumor predisposition syndrome, also known as hereditary leiomyomatosis and renal cell cancer (HLRCC), an autosomal-dominant syndrome characterized by cutaneous leiomyomata, uterine fibroids, and aggressive renal cell carcinoma (RCC)[709]. Pheochromocytoma and paraganglioma have also been described at lower frequency[710-711]. Whereas cutaneous leiomyomata appear at a mean age of 30 years, increasing in size and number with age, the age at diagnosis of uterine fibroids ranges from 18 to 53 years[711-712]. HLRCC has been associated with a 21% lifetime risk of RCC[713]. In the appropriate clinical context, germline testing of FH is recommended.

GENE
FUBP1

ALTERATION
I301fs*4

HGVS VARIANT
NM_003902.3:c.901dup (p.I301Nfs*4)

VARIANT CHROMOSOMAL POSITION
chr1:78429977

VARIANT ALLELE FREQUENCY (% VAF)
42.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

FUBP1 alteration has been reported in 1.5% of samples analyzed in COSMIC, with the highest incidences reported in tumors of the endometrium (3.6%), central nervous system (3.2%), large intestine (3.0%), skin (2.8%), stomach (2.7%), and liver (2.6%) (COSMIC, Feb 2023)[246]. One study reported higher expression of FUBP1 in colorectal carcinoma tissues compared to adenoma and normal colon epithelial tissues[714]. A genetic signature defined by concomitant alterations in IDH1, CIC, and FUBP1 is associated with longer survival in patients with glioma[715]. FUBP1 has been shown to activate the expression of MYC[716-719], activate p27KIP1[720], and regulate the splicing of MDM2[721].

FINDING SUMMARY

FUBP1 encodes far upstream element binding protein 1 (also called FBP-1), a DNA-binding protein reported to have roles in transcriptional activation and splicing regulation of target genes. It is believed to act as an oncogene in some tumor types, such as hepatocellular carcinoma and non-small-cell lung cancer[722-723], and as a tumor suppressor in others, particularly oligodendroglioma, for which mutations and/or loss of FUBP1 often co-occur with alterations in CIC or IDH1[715,724-727].

GENE
IRF2

ALTERATION
N167fs*7

HGVS VARIANT
NM_002199.3:c.500del (p.N167Mfs*7)

VARIANT CHROMOSOMAL POSITION
chr4:185329340-185329341

VARIANT ALLELE FREQUENCY (% VAF)
38.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to directly address genomic alterations in IRF2.

FREQUENCY & PROGNOSIS

Point mutations in the DNA binding domain of IRF2 have been identified in pancreatic cancer and have been shown to be inactivating[728]. Inactivating mutation or homozygous deletion of IRF2 has also been reported in 4/125 and 2/125 hepatocellular carcinoma (HCC) tumors, respectively, all 6 of which were hepatitis B virus (HBV)-related[729].

FINDING SUMMARY

IRF2 encodes the transcription factor interferon regulatory factor 2, which has been shown to regulate cellular responses to interferons, as well as cell growth and transformation.

GENE
KMT2D (MLL2)

ALTERATION
A221fs*40

HGVS VARIANT
NM_003482.4:c.661del (p.A221Lfs*40)

VARIANT CHROMOSOMAL POSITION
chr12:49447772-49447773

VARIANT ALLELE FREQUENCY (% VAF)
40.6%

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[229], and are especially prevalent in lung squamous cell carcinoma (SCC)[730] and small cell lung carcinoma (SCLC)[731]. 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[732]. 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])[733]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[734].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[735]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[736]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[737].

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[507-512]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[511,514-515]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
MAPK1

ALTERATION
R191H

HGVS VARIANT
NM_002745.4:c.572G>A (p.R191H)

VARIANT CHROMOSOMAL POSITION
chr22:22153338

VARIANT ALLELE FREQUENCY (% VAF)
37.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs that directly target ERK2, although ERK1/2 inhibitors are in clinical trials. In preclinical studies, ERK1/2 inhibitors have been shown to inhibit the activities of ERK2 mutations[738-740] or restore sensitivity to the EGFR inhibitor WZ4002 in a WZ4002-resistant cell line harboring MAPK1 amplification[741]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

MAPK1 mutations have been reported infrequently in solid and hematological malignancies, with highest incidences observed in liver (4.2%) and cervical (3.4%) cancers, and at lower frequencies in other tumor types (COSMIC, Dec 2022)[246]. MAPK activation (as assessed by ERK phosphorylation) has been frequently detected in glioblastoma tumors[742-744] and higher levels of activation correlated with increasingly inferior survival (high levels vs. medium levels vs. low levels)[742-743]. MAPK1-mediated activation of Wnt/beta-catenin signaling through osteopontin has been implicated in cholangiocarcinoma progression[745]. In addition, a MAPK1-associated SNP was correlated with increased risk of high-risk rectal cancer[746]. However, downregulation of MAPK1 was found to significantly associated with poorer disease free survival for HNSCC patients[747].

FINDING SUMMARY

MAPK1, also known as ERK2, encodes a mitogen-activated protein kinase family member that is involved in the transduction of proliferation and differentiation signals. MAPK1 mutations located in the binding site for ERK and FXFP, such as seen here, have been characterized as inactivating[739].

GENE
MLH1

ALTERATION
R127I

HGVS VARIANT
NM_000249.3:c.380G>T (p.R127I)

VARIANT CHROMOSOMAL POSITION
chr3:37045965

VARIANT ALLELE FREQUENCY (% VAF)
40.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MLH1 inactivation leads to MMR defects, high MSI, and increased mutational burden[26,68,748-749], which may predict response to the anti-PD-1 immunotherapies pembrolizumab and nivolumab[6-8]. In a Phase 2 study of pembrolizumab in MSI-high colorectal cancer (CRC), three patients with MLH1 (germline) mutations experienced one partial response and two stable diseases[7]. Pembrolizumab demonstrated a significantly higher objective response rate in MSI-high CRC compared with microsatellite stable CRC (40% vs. 0%)[7] and its efficacy correlated with high mutational burden in non-small cell lung cancer[8]. Nivolumab achieved a complete response in a patient with MSI-high CRC[6]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[750], potential biomarkers of response to anti-PD-1 immunotherapies. These therapies are in clinical trials for various tumor types and may be appropriate, particularly for hypermutant tumors. 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

MLH1 mutation has been reported in 0-1.6% of prostate carcinoma cases[54-55,57,59,75]. Approximately 12% (7/60) of prostate cancers were found to be hypermutated, with two of the hypermutated cases having MLH1 mutations[14]. MLH1 expression was shown to be reduced in approximately 50% of 39 prostate tumors analyzed in one study[751]. In another analysis, MLH1 nuclear expression was detected in 85% (6220/7275) prostate cancers; strong expression of MLH1 was observed in 55.2% of TMPRSS2-ERG-positive cases, but only in 32.9% of TMPRSS2-ERG-negative cases[752]. MLH1 expression was significantly associated with early biochemical recurrence in univariate analyses in one study[752].

FINDING SUMMARY

MLH1 encodes the protein MutL homolog 1, colon cancer, nonpolyposis type 2, which binds PMS2 to form MutLalpha, a complex involved in DNA mismatch repair (MMR)[753]. 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[22]. 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 MLH1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Lynch syndrome (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in MLH1 are associated with an autosomal dominant condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which is characterized by increased risk of a number of cancers[27]. Approximately 50% of Lynch syndrome-associated mutations have been attributed to alterations in MLH1[754]. Lynch syndrome accounts for 1-7% of all colorectal cancers and has an estimated prevalence in the general population between 1:600 and 1:2000[30-32]. In the appropriate clinical context, germline testing of MLH1 is recommended.

Electronically signed by Brennan Decker, M.D., Ph.D. | 04 June 2023
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GENE
MSH2

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MSH2 inactivation leads to MMR defects, MSI, and high mutational burden[14,18,755-757], which may predict response to the anti-PD-1 immunotherapies pembrolizumab and nivolumab[6-8]. In a Phase 2 study of MSI-high cancers, six patients with MSH2 (germline) mutations reported one partial response and two stable diseases[7]. Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-high CRC compared with microsatellite stable CRC (40% vs. 0%)[7] and its efficacy correlated with high mutational burden in non-small cell lung cancer[8]. Treatment with nivolumab resulted in a complete response in a patient with MSI-high CRC[6]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[750], potential biomarkers of response to PD-1 targeted immunotherapies. These therapies are in clinical trials for various tumor types and may be appropriate, particularly in hypermutant tumors.

— Nontargeted Approaches —

Preclinical studies have shown that tumor cells deficient in MSH2 are markedly sensitive to methotrexate in vitro[758]. Low levels of MSH2 have been observed by immunohistochemistry (IHC) in NSCLC and may predict benefit to cisplatin-based adjuvant chemotherapy[759-760].

FREQUENCY & PROGNOSIS

MSH2 mutations are rare in prostate carcinoma and have not been detected in this context in multiple datasets[54-55,57,75]. Deep deletion of MSH2 has been observed in ~1% of prostate carcinoma samples in large datasets[56,489]. Loss of MSH2 protein expression was detected in 1.2% (14/1176) of primary prostate cancer samples in 1 study; of these 14 samples that could be further analyzed, 12/12 samples had loss of function alterations in MSH2 which included biallelic inactivation or hypermutation[761]. A study of 59 patients with hormone-sensitive prostate cancer identified MSH2, CDK12, RB1, and TP53 alterations as independent risk factors for early progression to castration-resistant prostate cancer[215]. Multiple studies have correlated low or absent MSH2 expression with a decreased risk of recurrence and increased disease-free survival and OS in patients with prostate cancer[762-765].

FINDING SUMMARY

MSH2 encodes a DNA mismatch repair protein belonging to the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[22]. Alterations such as seen here may disrupt MSH2 function or expression[766-778].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in MSH2 are associated with an autosomal dominant condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which is characterized by increased risk of a number of cancers[27]. In one large study of Lynch syndrome, endometrial cancer was the most common cancer reported outside the colon, with an incidence of 13.8%[28]. For family members of patients with newly diagnosed endometrial cancer, the clinical utility of testing the patient for germline mutations in MMR genes is higher for mutations in MLH1 or MSH2 than it is for MSH6 or PMS2 mutations[779]. Therefore, in the appropriate clinical context, germline testing of MSH2 is recommended.

GENE
MSH3

ALTERATION
N385fs*19

HGVS VARIANT
NM_002439.3:c.1148dup (p.N385Qfs*19)

VARIANT CHROMOSOMAL POSITION
chr5:79970914

VARIANT ALLELE FREQUENCY (% VAF)
31.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies in the context of MSH3-deficient cancer cells have demonstrated antitumor efficacy of DNA-PKcs inhibitors[780] and PARP inhibitors such as olaparib[781] as well as increased chemosensitivity to cisplatin, oxaliplatin, and SN-38[781-782]. However, these remain to be tested in a clinical context.

FREQUENCY & PROGNOSIS

For patients with metastatic disease, MSH3 mutations have been reported with highest prevalence (4-5%) in colorectal (CRC) and endometrial cancers and are rare (<1%) in other tumor types such as prostate, lung, breast, ovarian, or pancreatic[593]. MSH3 loss has been correlated with the late development and progression of a variety of sporadic cancers including lung, ovarian, bladder, breast, and CRC tumors[783-787]. Certain germline polymorphisms in MSH3 have been associated with poor prognosis in CRC[787], head and neck squamous cell carcinoma (HNSCC)[788], non-small cell lung cancer (NSCLC)[789], and pancreatic cancer[790], while MSH3 loss was associated with improved post-surgery outcome in 1 study of patients with MLH1-deficient CRC[791].

FINDING SUMMARY

MSH3, while in the MutSβ heterodimer complex with MSH2, detects mismatched bases and participates in double-strand break repair by homologous recombination[780,792-794]. Inactivating MSH3 frameshift mutations may increase microsatellite instability (MSI) and lead to the production of elevated microsatellite alterations at selected tetranucleotide repeats (EMAST)[793,795], which have been recognized as a genomic signature in colorectal cancer (CRC) with MSI[796-797]. Certain germline polymorphisms in MSH3 have been reported to increase the risk of various cancers including CRC[798-803], breast[798,804], esophageal[805], prostate[798,806-807], gastric[808], and head and neck squamous cell carcinoma (HNSCC)[788].

GENE
MSH6

ALTERATION
loss

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[14,18,22,68,756-757]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[7,809] and nivolumab[6]. Higher mutation burden was also reported to be associated with response to pembrolizumab[8]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[750], 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 at low frequencies in prostate adenocarcinoma, in up to 1% of cases across several studies[54-55,57,75]. In one study, 10% (5/50) of primary advanced prostate cancer samples analyzed were reported to be hypermutated and characterized by MSI; of these hypermutated tumors, 4/5 harbored inactivating mutations in MSH6 and/or MSH2 and loss of MSH6 and/or MSH2 protein expression[14]. Published data investigating the prognostic implications of MSH6 alterations in prostate cancer are limited (PubMed, Oct 2022).

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[22]. Alterations such as seen here may disrupt MSH6 function or expression[810-815].

POTENTIAL GERMLINE IMPLICATIONS

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[30]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[754]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[29]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[30-32]. 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[816-820]. Given the association between MSH6 and these inherited syndromes, in the appropriate clinical context, germline testing of MSH6 is recommended.

GENE
NOTCH3

ALTERATION
G463*

HGVS VARIANT
NM_000435.2:c.1387G>T (p.G463*)

VARIANT CHROMOSOMAL POSITION
chr19:15299151

VARIANT ALLELE FREQUENCY (% VAF)
42.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[821], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[822-824]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[825]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[826]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

NOTCH3 mutations have been reported in up to 2% of metastatic prostate cancers[57,59] but not in two other studies of prostate adenocarcinoma[54,56]. NOTCH3 amplification or overexpression has been associated with poor clinicopathological features in prostate carcinoma, although the role of NOTCH signaling in this disease is complex[827-828].

FINDING SUMMARY

NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[829-830]. Alterations that disrupt or remove the transmembrane domain (amino acids 1644-1664), RAM domain (amino acids 1665-1837), and/or ANK repeats region (amino acids 1838-2000), which are necessary for the transcriptional activity of NOTCH family proteins, as well as internal deletions that remove EGF repeats (7-10 and 21-22), have been shown in vitro to negatively affect ligand binding and reduce NOTCH3 transcriptional activity and are predicted to be inactivating[830-834].

GENE
NTRK2

ALTERATION
A11V

HGVS VARIANT
NM_006180.3:c.32C>T (p.A11V)

VARIANT CHROMOSOMAL POSITION
chr9:87285695

VARIANT ALLELE FREQUENCY (% VAF)
41.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data indicate that NTRK fusions predict sensitivity to TRK inhibitors such as larotrectinib, entrectinib, AZD7451, belizatinib, and PLX7486[835-845]. In a Phase 1 study, the activity of larotrectinib was limited in patients who harbored NTRK amplification and not observed in patients with NTRK mutations in the absence of fusion[835]. A case study of a patient with esophageal carcinoma who harbored NTRK1 amplification reported a short PR[846]. 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

NTRK2 mutation was detected in 8.6% of prostate carcinoma samples in COSMIC (Jun 2023)[246]. Published data investigating the prognostic implications of NTRK2 alterations in prostate cancer are limited (PubMed, Jan 2023).

FINDING SUMMARY

NTRK2 encodes neurotrophic tyrosine kinase receptor type 2 (TRKB), also known as tropomyosin-related kinase B. TRKB is a receptor for brain-derived neurotrophic factor (BDNF), and neurotrophin-4 and is a member of the insulin receptor subfamily[847-848]. TRKB activates the RAS-ERK and PI3K-AKT signaling pathways, regulating cell survival, proliferation, and differentiation in normal and neoplastic cells[847,849-851]. Overexpression of TRKB promotes malignant transformation, cell invasiveness, and tumor metastasis, thereby suggesting a role for NTRK2 as an oncogene[852]. 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
PMS2

ALTERATION
Y268fs*39

HGVS VARIANT
NM_000535.4:c.802del (p.Y268Tfs*39)

VARIANT CHROMOSOMAL POSITION
chr7:6036957-6036958

VARIANT ALLELE FREQUENCY (% VAF)
46.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Defective MMR that occurs because of mutation(s) in the MMR family, which includes MLH1, MSH2, MSH6, and PMS2, can result in microsatellite instability (MSI), which is common in colon, endometrial, and stomach cancers[22]. Alterations in PMS2 can lead to impaired MMR activity[853], and selective loss of PMS2 by either mutation or loss of expression has been reported in colorectal cancer and endometrial cancer with MSI-high phenotype[757,854-855]. Clinical studies have shown that MSI predicts patient responses to the anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[7,809] and nivolumab[6], and alterations resulting in PMS2 functional loss may predict sensitivity to anti-PD-1 immune checkpoint inhibitors. However, this has not been directly demonstrated.

FREQUENCY & PROGNOSIS

PMS2 deletion or amplification have been each detected in <0.5% of analyzed prostate carcinomas, and PMS2 mutations have been detected in up to 1% of prostate cancer samples (cBioPortal, COSMIC, Sep 2022)[176-177,246]. Alterations in MMR genes, including PMS2, associated with increased risk of certain cancers, including prostate carcinoma[856], although data regarding the role of PMS2 in this tumor type are conflicting. Reduced PMS2 expression has been associated with poorly differentiated tumors and more aggressive prostate cancer[751,857-859]. Increased PMS2 expression has been associated with genetic instability and decreased time to recurrence in prostate cancer[860-861]. Restoring PMS2 expression had a protective effect in a PMS2-deficient preclinical model of prostate cancer, primarily through increased apoptosis[862].

FINDING SUMMARY

PMS2 encodes an endonuclease that has been shown to play a critical role in DNA mismatch repair (MMR) and apoptotic responses to DNA damage[863]. Both abnormally high levels of PMS2, caused by protein overexpression, and inactivating mutation leading to loss of PMS2 activity have been shown to result in genomic instability, resistance to genotoxic chemotherapy, and increased tumorigenicity in vivo[864-865]. Alterations such as seen here may disrupt PMS2 function or expression[853,866-870].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the PMS2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Lynch syndrome (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline PMS2 mutations have been associated with autosomal dominant Lynch syndrome and the rarer autosomal recessive Turcot syndrome[871-873]. Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) accounts for 1-7% of all colorectal cancers[30-31]. One study reported germline PMS2 mutation in 62% (61/99) of patients diagnosed with Lynch syndrome-associated tumors[867]. Turcot syndrome is characterized by concurring primary brain tumors and colon cancers and/or colorectal adenomas in pediatric patients[874]. Therefore, in the appropriate clinical context, germline testing of PMS2 is recommended.

GENE
PRKAR1A

ALTERATION
Q275*

HGVS VARIANT
NM_212472.1:c.823C>T (p.Q275*)

VARIANT CHROMOSOMAL POSITION
chr17:66525064

VARIANT ALLELE FREQUENCY (% VAF)
39.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in PRKAR1A. Preclinical studies have shown that depletion of PRKAR1A may sensitize cells to mTOR inhibitors such as rapamycin[875-876] or TKIs targeting SRC such as dasatinib[877].

FREQUENCY & PROGNOSIS

PRKAR1A mutations have been reported in less than 1% of solid tumor types and less than 0.5% of hematologic cancer samples analyzed in the COSMIC database (2023)[246]. Small studies of melanotic schwannoma, a rare tumor that can be sporadic or associated with Carney complex, have identified PRKAR1A mutation in 100% (12/12)[878] and loss of protein expression in 33% (7/21)[879] of cases. Published data investigating the prognostic implications of PRKAR1A alterations in cancer are limited (PubMed, Jan 2023). One small study reported that low tumor PRKAR1A protein expression was associated with reduced OS in patients with lung adenocarcinoma (HR=1.880)[880].

FINDING SUMMARY

PRKAR1A encodes a regulatory subunit of cyclic AMP-dependent protein kinase[881]. PRKAR1A is thought to be a tumor suppressor, and inactivating germline mutations and deletions are associated with Carney complex, an autosomal dominant syndrome characterized by increased risk of primary pigmented nodular adrenocortical disease, cardiac and other myxomas, endocrine tumors, and schwannomas[882-886]. Somatic PRKAR1A mutations have also been reported in cardiac myxoma[887-889].

GENE
QKI

ALTERATION
K134fs*14, R124*

HGVS VARIANT
NM_006775.2:c.401del (p.K134Rfs*14),
NM_006775.2:c.370C>T (p.R124*)

VARIANT CHROMOSOMAL POSITION
chr6:163899919-163899920, chr6:163899896

VARIANT ALLELE FREQUENCY (% VAF)
83.2%, 40.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies approved or in clinical trials that directly address genomic alterations in QKI.

FREQUENCY & PROGNOSIS

Recurrent deletions of QKI have been reported in astrocytomas and glioblastomas[890-892]. Decreased expression of quaking has also been reported in colon and gastric cancer, largely due to QKI promoter hypermethylation; in one study, forced expression of quaking in colon cancer cells inhibited proliferation and tumorigenesis[893-894]. However, another study reported that QKI acts as an oncogene in breast cancer by repressing the expression of the tumor suppressor FOXO1[895].

FINDING SUMMARY

QKI encodes quaking, an RNA-binding protein that plays roles in RNA metabolism and signal transduction and is necessary for myelination and embryonic development[896-897]. QKI acts as a negative regulator of cell-cycle progression[898].

GENE
SETD2

ALTERATION
R1407fs*5

HGVS VARIANT
NM_014159.6:c.4219del (p.R1407Gfs*5)

VARIANT CHROMOSOMAL POSITION
chr3:47161906-47161907

VARIANT ALLELE FREQUENCY (% VAF)
37.4%

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[899]. SETD2 has been associated with favorable prognosis in gastric cancer[900]. SETD2 has also been associated with poor prognosis in RCC and MDS[901-902], while data in other tumor types is limited (PubMed, Jun 2023).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[903] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[904]. 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[905]. SETD2 alterations such as observed here have been shown to be inactivating[906-911].

GENE
SMAD4

ALTERATION
G386S - subclonal

HGVS VARIANT
NM_005359.5:c.1156G>A (p.G386S)

VARIANT CHROMOSOMAL POSITION
chr18:48593405

VARIANT ALLELE FREQUENCY (% VAF)
4.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SMAD4. Preclinical studies in colorectal cancer have reported associations of SMAD4 inactivation or loss with sensitivity to inhibitors of Aurora kinase A[912] and the Wnt/beta-catenin pathway[913].

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with improved responses to chemotherapeutic agents in patients with pancreatic cancer[914-916] and non-small cell lung cancer (NSCLC)[917]. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy[918] and adjuvant chemoradiotherapy[919].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[920], pancreatic acinar cell carcinoma (26%)[921], cholangiocarcinoma (25%)[922], small intestine cancer (20%)[923], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[924-925], colorectal adenocarcinoma (CRC; 14%)[68], esophageal adenocarcinoma (14%)[926], and stomach adenocarcinoma (13%)[462]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[927] and intraductal papillary mucinous neoplasms (IPMN)[928]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[929]. SMAD4 gene alterations have been associated with reduced OS for patients with pancreatic adenocarcinoma[930]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[931-933], appendiceal mucinous neoplasm[934], gastric adenocarcinoma[935-936], esophageal adenocarcinoma[937], esophageal squamous cell carcinoma[938], breast cancer[939], and prostate cancer[940].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[941-942]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[943-956].

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[957-959], which is associated with an increased risk of gastrointestinal cancers[960]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[961]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

GENE
SPEN

ALTERATION
K1999fs*23

HGVS VARIANT
NM_015001.2:c.5996del (p.K1999Rfs*23)

VARIANT CHROMOSOMAL POSITION
chr1:16258726-16258727

VARIANT ALLELE FREQUENCY (% VAF)
37.4%

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 mutations.

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the MSK-MET dataset identified SPEN alterations in 1.2% of all samples[593]. SPEN truncating mutations have been reported at a higher frequency in adenoid cystic carcinoma (ACC; 21%)[962] and splenic marginal zone lymphoma (SMZL; 5%)[963].

FINDING SUMMARY

SPEN (also known as MINT or SHARP) encodes a transcriptional regulator that interacts with histone deacetylase 1 (HDAC1) and the silencing mediator for retinoid and thyroid receptors/nuclear receptor corepressor (SMRT/NcoR)[964-965] and represses the transcriptional activity of the NOTCH signaling pathway[966-967]. SPEN alterations that result in the disruption of functional domains (aa 2804-2816 or aa 3498-3664) are likely to be inactivating[965-967].

GENE
TGFBR2

ALTERATION
R497* - subclonal

HGVS VARIANT
NM_003242.5:c.1489C>T (p.R497*)

VARIANT CHROMOSOMAL POSITION
chr3:30729968

VARIANT ALLELE FREQUENCY (% VAF)
6.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies in development or in use for patients with inactivating mutations of TGFBR2. TGFBR2 activating mutations may predict sensitivity to therapies targeting TGFBR2, such as Lucanix and IMC-TR1, which have been in development and are in clinical trials in certain tumor types, but are not currently recruiting patients[968-972]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

TGFBR2 deletions or mutations have been reported in each 0-1% of prostate adenocarcinomas[54,56,59]. Down-regulation of TGFBR2 protein has been observed in 12/20 high-grade prostatic intraepithelial neoplasia and 36/60 prostate cancers[973]. Published data investigating the prognostic implications of TGFBR2 in prostate carcinoma are limited (PubMed, Sep 2022). Conditional knockout of TGFBR2 in stromal fibroblastic cells in a transgenic mouse model results in prostatic intraepithelial neoplasia and adenocarcinoma[974].

FINDING SUMMARY

TGFBR2 encodes a type 2 receptor for transforming growth factor-beta (TGF-beta)[975]. Loss of TGF-beta signaling results in insensitivity to the growth inhibitory effects of TGF-beta and ultimately causes an increase in cellular growth and transformation[976]. Constitutive activation of TGFBR2 has been reported to increase the invasive behavior of carcinoma cells[969]. TGFBR2 R497* is predicted to be inactivating[977-980].

POTENTIAL GERMLINE IMPLICATIONS

The TGFBR2 R497* variant observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters) associated with Loeys-Dietz syndrome (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TGFBR2 are associated with hereditary nonpolyposis colorectal cancer (HNPCC) type 6[981] and the autosomal dominant disorder Loeys-Dietz syndrome type 2[980,982-984]. Both disorders are rare, with no clear prevalence data reported; HNPCC type 6 has only been described in one case report[981] and Loeys-Dietz syndrome type 2 is also rarely reported[985]. However, in the appropriate clinical context, germline testing of TGFBR2 is recommended.

GENE
TP53

ALTERATION
R196*, Y205H - subclonal, R175C

HGVS VARIANT
NM_000546.4:c.586C>T (p.R196*),
NM_000546.4:c.613T>C (p.Y205H),
NM_000546.4:c.523C>T (p.R175C)

VARIANT CHROMOSOMAL POSITION
chr17:7578263, chr17:7578236, chr17:7578407

VARIANT ALLELE FREQUENCY (% VAF)
41.2%, 0.78%, 39.3%

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[986-989] or p53 gene therapy such as SGT53[990-994]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[995]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[996]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[997]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[998]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[999]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[1000]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[1001]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[994]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[1002]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[1003].

— Nontargeted Approaches —

In post-hoc analyses of a Phase 1/2 trial, the addition of carboplatin to cabazitaxel significantly improved PFS (6.0 vs. 2.2 months) and OS (17.4 vs. 9.9 months) for patients with an aggressive variant prostate cancer molecular signature (AVPC-MS, composed of alterations in at least 2 of the genes RB1, TP53, and PTEN); no significant difference in outcomes were observed for patients lacking this signature (NCCN Prostate Cancer Guidelines, v1.2023)[395]. Post-hoc analysis of a Phase 2 trial in metastatic castration-resistant prostate cancer suggests that patients with aggressive variant prostate cancer (AVPC), molecularly characterized by harboring alterations in at least 2 genes of TP53, RB1, and PTEN, as seen in this sample, may benefit from cabazitaxel combined with carboplatin compared with cabazitaxel alone (median PFS of 5.1 vs. 2.2 months, p=0.03; estimated median OS of 11.2 vs. 10.5 months, p=0.11), whereas patients who were AVPC-negative did not benefit from the more intense chemotherapy combination in this study[395].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 18-40% of prostate cancers[350,1004]. A study of 59 patients with hormone-sensitive prostate cancer identified MSH2, CDK12, RB1, and TP53 alterations as independent risk factors for early progression to castration-resistant prostate cancer[215]. Overexpression of p53, which is indicative of TP53 dysregulation, has been reported to be significantly more common in late-stage and hormone-refractory prostate cancers and has been found to be associated with prostate-specific antigen (PSA) recurrence in low- and intermediate-grade prostate cancer[1005]. TP53 loss has been found to be associated with prostate cancer-specific mortality in univariate analysis[1006]. Concurrent alterations in at least 2 of the TP53, RB1, and PTEN genes, as seen in this sample, molecularly define a subtype of prostate cancer with aggressive clinical course and reduced sensitivity to androgen-deprivation therapies (NCCN Prostate Cancer Guidelines, v1.2023)[395,401-404].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[1007]. Alterations such as seen here may disrupt TP53 function or expression[1008-1012].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Apr 2023)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[1013-1015], including sarcomas[1016-1017]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[1018] to 1:20,000[1017]. 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[1019]. 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[507-512]. 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[507-508]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[513]. Comprehensive

genomic profiling of solid tumors detects nontumor alterations that are due to CH[511,514-515]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE

XRCC2

ALTERATION
L117fs*17

HGVS VARIANT
NM_005431.1:c.350del (p.L117Wfs*17)

VARIANT CHROMOSOMAL POSITION
chr7:152346219-152346220

VARIANT ALLELE FREQUENCY (% VAF)
37.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to directly target XRCC2 inactivation. However, loss of functional XRCC2 is associated with increased sensitivity to DNA cross-linking agents such as mitomycin C and to ionizing radiation[1020-1022].

FREQUENCY & PROGNOSIS

XRCC2 mutation has been seen in 2.4% of colorectal adenocarcinomas[68], 2.4% of stomach adenocarcinomas[462], and 1.3% of uterus corpus endometrioid carcinomas[65]. High-level amplification of XRCC2 has been reported in 4.7% of ovarian serous cystadenocarcinomas[1023], 3.9% of lung adenocarcinomas[1024], and 1.8% of glioblastomas[1025], whereas homozygous deletion of XRCC2 has been seen in 3.1% of acute myeloid leukemias[1026], 3% of esophagus-stomach cancers[1027], and 1.4% of head and neck squamous cell carcinomas[524]. Alterations in other tumor types are more rarely observed (cBioPortal, Jan 2023)[176-177]. XRCC2 polymorphisms, including R188H, have been associated with low penetrance risk of developing breast cancer[1028-1030]; however, these findings are controversial, with some studies instead showing a protective effect[1031-1036]. XRCC2 polymorphisms have also been implicated in decreased survival in the context of pancreatic[1037-1038], lung[1039], and rectal[1040] cancers but reduced risk of bladder[1041] and ovarian[1036] cancers.

FINDING SUMMARY

XRCC2 encodes a RAD51 homolog involved in homologous recombination; in complex with RAD51 proteins, XRCC2 enables the repair of DNA double-strand breaks caused by genotoxic stresses such as DNA cross-linking agents and ionizing radiation[1020,1022,1042-1046]. Alterations that disrupt the Walker A (residues 48-55) or Walker B (residues 145-149) motifs, or the C-terminal region of XRCC2 involved in RAD51 binding, disrupt homologous recombination by XRCC2[1021,1028,1047]. The missense mutations R91W, I95L, C120Y, L133P, R188C, and E207G also impair XRCC2 function, although to a lesser extent than alterations leading to premature protein truncation[1047].

Dostarlimab

Assay findings association

CDK12
R1048*, N474fs*8 - subclonal

Microsatellite status
MSI-High

Tumor Mutational Burden
350 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[34-36,49,1048] , 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[34-35] . On the basis of limited clinical evidence in prostate cancer, including multiple prostate-specific antigen (PSA) responses, CDK12 inactivating alterations may predict sensitivity to PD-1 inhibitors[194,1049-1050] . On the basis of prospective clinical data showing efficacy of dostarlimab against various microsatellite instability-high (MSI-H) solid tumors[9,1051-1053] , MSI-H status may predict sensitivity to dostarlimab.

SUPPORTING DATA

Clinical data on the efficacy of dostarlimab for the treatment of prostate cancer are limited (PubMed, Mar 2023). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[9,1052,1054] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[1052,1055] .

Olaparib

Assay findings association

BARD1
R406*

BRCA2
D946fs*14

BRIP1
splice site 918+1G>A - subclonal

CDK12
R1048*, N474fs*8 - subclonal

CHEK1
T226fs*14

FANCL
G119*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[85,245,1056], breast[175], endometrial[1057], and prostate cancer[174], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in ovarian cancer[70,245], FANCL loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in prostate[80,174,210,1058-1059], loss or inactivation of genes that are involved in homologous recombination repair may confer sensitivity to PARP inhibitors. CHEK1 inhibition has been associated with sensitivity to PARPi in preclinical studies[224,1060]. On the basis of extensive clinical evidence in ovarian cancer[89-93] as well as strong clinical evidence in multiple other cancer types[79-81,89,92,96,1061], loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib. On the basis of preclinical evidence[71,74] and clinical evidence in ovarian cancer[70], BARD1 loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of limited clinical benefit in prostate[209-210,1062] and ovarian[1063] cancer, CDK12 inactivating alterations may confer sensitivity to PARP inhibitors.

SUPPORTING DATA

The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (mCRPC) reported improved radiographic PFS (rPFS; 7.4 vs. 3.6 months, HR=0.34) and median OS (mOS; 19.1 vs. 14.7 months, HR=0.69) with olaparib compared with physician's choice of abiraterone plus prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations[209,1064]. For patients with other homologous recombination repair (HRR) gene alterations, PFS (4.8 vs. 3.3 months, HR=0.88) and mOS (14.1 vs. 11.5 months, HR=0.96) were numerically increased with olaparib[1064]. Other studies, including the Phase 2 TOPARP-A and TOPARP-B studies, reported similar results[80,210,1065]. In a real-world study of olaparib and/or rucaparib for heavily pretreated prostate cancer, patients with pathogenic BRCA2 mutations experienced greater benefit than patients with other HRR mutations (median PFS of 7.2 vs. 2.8 months, p=0.291; 30% decrease in prostate-specific antigen of 69% vs. 4.0%, p<0.001)[1066]. In the Phase 3 KEYLYNK-010 study for patients with pretreated mCRPC, treatment with olaparib plus pembrolizumab did not lead to significantly improved rPFS (4.4 months vs. 4.2 months, HR=1.02) or OS (15.8 months vs. 14.6 months, HR=0.94)[1067]. Benefits were also seen in Phase 1 or 2 studies of olaparib in combination with durvalumab[1068], pembrolizumab[1069-1070], or the ATP inhibitor ceralasertib[1071] for patients with prostate cancer. PROfound patients with BRCA1/2 or ATM alterations also had improved ORR (33.3% [28/84] vs. 2.3% [1/43], p<0.001) with olaparib compared with physician's choice of enzalutamide or abiraterone/prednisone[209]. A Phase 2 trial of olaparib for patients with germline BRCA1/2 mutation reported 50% (4/8) PRs and 25% (2/8) SDs for patients with previously treated prostate cancer[79]. In the Phase 3 PROpel study for patients with metastatic castration-resistant prostate cancer, treatment with first-line olaparib plus abiraterone and prednisone led to significantly improved rPFS (not reached vs. 8.4 months, HR=0.23) in patients with BRCA1 and BRCA2 mutations compared with placebo[1072]. PROfound patients with CDK12 alterations treated with olaparib experienced numerically improved PFS (5.1 vs. 2.2 months) and OS (14.1 vs. 11.5 months, HR=0.97) compared with physician's choice of abiraterone/prednisone or enzalutamide[209]. The Phase 2 TOPARP-B study reported reduced circulating tumor cell levels for 41.7% (5/12) of patients with CDK12-altered mCRPC treated with olaparib, but no PSA50 or objective responses[210]. In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)[1073].

Olaparib + Abiraterone

Assay findings association

BRCA2
D946fs*14

AREAS OF THERAPEUTIC USE

Olaparib is a PARP inhibitor, and abiraterone is an orally available CYP17 inhibitor. These 2 therapies in combination together with prednisone or prednisolone are FDA approved to treat patients with BRCA1/2-mutated metastatic castration-resistant prostate cancer.

GENE ASSOCIATION

On the basis of clinical evidence in prostate cancer[1074-1078], inactivation of either BRCA1 or BRCA2 may confer sensitivity to the combination of a PARP inhibitor and abiraterone.

SUPPORTING DATA

The Phase 3 PROpel study assessed first-line olaparib plus abiraterone and prednisone for patients with metastatic castration-resistant prostate cancer (mCRPC) and reported improved median radiographic PFS (rPFS) (27.6 vs. 16.4 months, HR=0.61) and improved median OS (42.1 vs. 34.7 months, HR=0.81) compared with abiraterone, prednisone, and placebo; greater benefit was observed among patients with homologous recombination repair (HRR) mutations for both rPFS (NR vs. 13.9 months, HR=0.50) and OS (NR vs. 28.5 months, HR=0.66), than patients without HRR mutations (rPFS: 24.1 vs. 19.0 months, HR=0.76; OS: 42.1 vs. 38.9 months, HR=0.89)[1074-1075]. For patients with mCRPC harboring inactivating germline or somatic alterations in BRCA1, BRCA2, and/or ATM, the triple combination of olaparib with abiraterone and prednisone improved median PFS (not reached vs. 11.3 or 10.4 months, respectively) relative to single-agent olaparib or abiraterone plus prednisone in the Phase 2 BRCAAway trial[1076]. Another Phase 2 study comparing olaparib or placebo combined with abiraterone and prednisone or prednisolone for patients with mCRPC who had progressed on chemotherapy reported similar results, with median rPFS of 13.8 months and 8.2 months, respectively (HR=0.65, p=0.034)[1079].

Pembrolizumab

Assay findings association

CDK12
R1048*, N474fs*8 - subclonal

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of limited clinical evidence in prostate cancer, including multiple prostate-specific antigen (PSA) responses, CDK12 inactivating alterations may predict sensitivity to PD-1 inhibitors[194,1049-1050] . On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against MSI-H or mismatch repair-deficient (dMMR) solid tumors[7,1080-1084] , MSI-H status may predict sensitivity to pembrolizumab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

For patients with prostate cancer enrolled in various clinical trials, Tumor Mutational Burden (TMB) of 10 Muts/Mb or higher was associated with an ORR of 9.1% (1/11) on pembrolizumab, whereas a lower TMB was associated with an ORR of 6% (n=115)[1085]. A case study described a patient with POLE-mutant prostate cancer and high TMB who experienced progression on prior treatment and exhibited a durable response from pembrolizumab[1086]. In a retrospective study of patients with CDK12-mutated mCRPC receiving fourth to sixth line pembrolizumab or nivolumab, a median PFS of 5.4 months and 33.3% (3/9) prostate-specific antigen (PSA) response rate were reported[198]. In another retrospective study of patients with CDK12-mutated mCRPC, a 10.5% (2/19) rate of PSA decline greater than 50% (PSA50) and mPFS of 2.8 months following immunotherapy (15/19 pembrolizumab) treatment were reported[1050]. In the Phase 3 KEYNOTE-921 trial, the addition of pembrolizumab to docetaxel did not significantly improve radiographic PFS (rPFS; 8.6 vs. 8.3 months, HR=0.85) or median OS (mOS; 19.6 vs. 19.0 months, HR=0.92) compared with docetaxel for patients with metastatic castration-resistant prostate cancer (mCRPC)[1087]. In the KEYNOTE-199 and -365 trials, patients with mCRPC treated with pembrolizumab plus enzalutamide experienced a prostate-specific antigen (PSA) decrease ≥50% (PSA50) of 8.8-23% and a DCR of 32-51%; an ORR of 12.0-12.3% was reported for patients who were Response Evaluation Criteria in Solid Tumors (RECIST) measurable[1088-1089] . Within the pembrolizumab monotherapy arms of KEYNOTE-199, patients with mCRPC reported a 13-39% DCR and an mOS of 7.9-14.1 months between all cohorts[1090]. In another cohort of KEYNOTE-365, patients with mCRPC treated with pembrolizumab plus olaparib achieved a confirmed PSA response rate of 15% (15/102), median rPFS of 4.5 months, and mOS of 14 months; an ORR of 8.5% (5/59 PRs) was reported for patients with RECIST-measurable disease and was generally consistent across PD-L1 and homologous recombination repair subgroups[1091]. A Phase 1b study for small cell cancer of the urothelium and neuroendocrine cancer of the prostate (NECP) reported an ORR of 43% (3/7) and a 36% PFS rate at 12 months in the NECP cohort following treatment with pembrolizumab in combination with chemotherapy[1092]. One case study reported durable PR to pembrolizumab for 1 patient with metastatic platinum-refractory small cell carcinoma of the prostate[1093].

Rucaparib

Assay findings association

BARD1
R406*

BRCA2
D946fs*14

BRIP1
splice site 918+1G>A - subclonal

CDK12
R1048*, N474fs*8 - subclonal

CHEK1
T226fs*14

FANCL
G119*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in ovarian cancer[70,245] , FANCL loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in prostate[80,174,210,1058-1059] , loss or inactivation of genes that are involved in homologous recombination repair may confer sensitivity to PARP inhibitors. CHEK1 inhibition has been associated with sensitivity to PARPi in preclinical studies[224,1060] . On the basis of preclinical evidence[71,74] and clinical evidence in ovarian cancer[70], BARD1 loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of strong clinical evidence in ovarian cancer[85-86,996] , as well as clinical data in other cancer types[86,1094-1095] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib. On the basis of clinical evidence in ovarian[85,245,1056] , breast[175], endometrial[1057], and prostate cancer[174], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. On the basis of limited clinical benefit in prostate[209-210,1062] and ovarian[1063] cancer, CDK12 inactivating alterations may confer sensitivity to PARP inhibitors.

SUPPORTING DATA

The Phase 3 TRITON3 study of rucaparib for patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) and BRCA alterations reported an improved radiographic PFS (10.2 vs. 6.4 months, HR=0.61) and median OS (mOS; 23.6 vs. 20.9 months, HR=0.94) compared to physician's choice docetaxel or second-generation androgen receptor pathway inhibitors (ARPIs). Patients with chemotherapy-naive mCRPC and ATM alterations reported slightly improved radiographic PFS (8.1 vs. 6.8 months, HR=0.95) compared to physician's choice docetaxel or second-generation ARPI[1096]. The Phase 2 TRITON2 study of rucaparib for patients with mCRPC and deleterious DNA-repair gene alterations reported an ORR of 44% (27/62; 7 CRs) and radiographic PFS of 9.0 months[1097]. Objective responses were reported for patients with ATM, BRIP1, CHEK2, FANCA, PALB2, and RAD51B alterations[174]. In a real-world study of olaparib and/or rucaparib for heavily pretreated prostate cancer, patients with pathogenic BRCA2 mutations experienced greater benefit than patients with other homologous recombination repair mutations (median PFS 7.2 vs. 2.8 months, p=0.291; PSA30 69.2% vs. 4.0%, p<0.001)[1066]. The Phase 1b/2 BrUOG360 study of rucaparib combined with copanlisib to treat patients with mCRPC achieved a confirmed prostate-specific antigen (PSA) ≥50% decline for 2 patients (22% [2/9]), 1 of whom had a BRCA2 loss and 1 of whom had a PALB2 alteration[1098]. A Phase 1b study of rucaparib combined with ipatasertib for patients with mCRPC reported a PSA ≥50% decline rate of 35% (9/26) and an mOS of 13.3 months[1099].

Atezolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) as well as adult and pediatric patients 2 years and older with alveolar soft part sarcoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data showing efficacy of atezolizumab alone or in combination with antiangiogenic therapy for patients with MSI-H colorectal cancer[1100] or endometrial cancer[1101], MSI-H status may predict sensitivity to atezolizumab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

A Phase 1 study evaluating atezolizumab monotherapy for patients with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) reported limited efficacy, with only 4% (1/25) of patients achieving PR and 8.6% (3/35) of patients with a confirmed prostate-specific antigen (PSA) response, a PFS of 2.7 months, and median OS (mOS) of 14.7 months[1102]. The Phase 3 IMbassador250 study evaluating atezolizumab and enzalutamide versus enzalutamide alone failed to meet its primary endpoint of OS (HR=1.12) for patients with mCRPC previously treated with abiraterone; no differences were observed for radiographic PFS (HR=0.90) or time to PSA progression (HR=1.04) between treatment groups, though an increase in responders was observed in the atezolizumab arm (12% vs. 6.7% PRs)[1103]. The COSMIC-021 Phase 1b trial of atezolizumab plus cabozantinib for patients with mCRPC reported an ORR of 23% (3 CRs, 28 PRs), DCR of 84%, mOS of 18.4 months, and median PFS of 5.5 months[1104]. Another Phase 1 study investigating combination treatment of atezolizumab and the IDO1-inhibitor navoximod observed 1 PR and 2 PDs for patients with prostate cancer[1105]. In the prospective Phase 2a MyPathway basket study evaluating atezolizumab for patients with TMB-High solid tumors, patients with TMB ≥16 Muts/Mb achieved improved ORR (38% [16/42] vs. 2.1% [1/48]), DCR (62% [26/42] vs. 23% [11/48]), mPFS (5.7 vs. 1.8 months, HR 0.34), and mOS (19.8 vs. 11.4, HR 0.53) as compared to those with TMB ≥10 and <16 Muts/Mb[46]. 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%)[49].

Avelumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[1100], endometrial cancer[1101], or gastric/gastroesophageal junction cancer[1106], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

A Phase 2 trial of avelumab in combination with radiotherapy for patients with metastatic castration-resistant prostate cancer (mCRPC) reported an ORR of 31% (5/16) with median PFS and median OS of 8.4 months and 14.1 months, respectively[1107]. A trial of avelumab in combination with androgen receptor antagonists for patients with mCRPC who had progressed on previous treatment reported durable SD >24 weeks for 39% (7/18) of patients[1108]. 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)[1109], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[1110], urothelial carcinoma[1111], mesothelioma[1112], ovarian carcinoma[1113], and breast cancer[1114], and from avelumab combined with axitinib in renal cell carcinoma[1115]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved ORR, PFS, or OS in NSCLC in the first-line setting and in ovarian and breast cancer[1109,1113-1114] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[1116-1118] .

Cemiplimab

Assay findings association

CDK12
R1048*, N474fs*8 - subclonal

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of limited clinical evidence in prostate cancer, including multiple prostate-specific antigen (PSA) responses, CDK12 inactivating alterations may predict sensitivity to PD-1 inhibitors[194,1049-1050] . On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[3,6-7,1080-1083] , MSI-H status may predict sensitivity to cemiplimab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of prostate carcinoma are limited (PubMed, Mar 2023). Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[1119]. 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[1120-1121] . 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[1122].

Durvalumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[1100], endometrial cancer[1101], or gastric/gastroesophageal junction cancer[1106], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

A randomized Phase 2 study of durvalumab for patients with metastatic castration-resistant prostate cancer (mCRPC) reported an ORR of 0% (0/13)[1123]. Another Phase 2 study of durvalumab in combination with the PARP inhibitor olaparib reported prostate-specific antigen decline ≥50% for 53% (9/17) of patients with mCRPC who had progressed on enzalutamide and/or abiraterone; 24% (4/17) of the patients experienced radiographic responses, median radiographic PFS was 16.1 months, and 12-month PFS probability for patients with or without mutations in DNA damage repair genes was 83% and 36%, respectively (p=0.03)[1068]. A Phase 2 study for patients with mCRPC reported a low response rate of 3.4% (1/29), median radiographic PFS of 2.3 months, and median OS of 10.7 months with treatment of durvalumab combined with adenosine 2A receptor inhibitor AZD4635[1124]. In a case report, a patient with prostate sarcoma achieved a PR on durvalumab[1125]. A case study reported no responses for 2 patients with prostate neuroendocrine tumor treated with durvalumab combined with cabazitaxel[1126].

Durvalumab + Tremelimumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses; tremelimumab is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibody. These therapies are FDA approved in combination to treat adult patients with unresectable hepatocellular carcinoma and metastatic non-small cell lung cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[10-11,1127-1128] , microsatellite instability high (MSI-H) status may predict sensitivity to combination durvalumab and tremelimumab.

SUPPORTING DATA

A randomized Phase 2 study of durvalumab in combination with tremelimumab for patients with metastatic castration-resistant prostate cancer (mCRPC) reported an ORR of 16% (6/37), with 38% (5/13) of PD-L1+ (≥1%) and 5% (1/19) of PD-L1- disease responding[1123]. Another Phase 2 study of this therapy combination reported that 12% (3/25) and 4% (1/25) of patients with mCRPC who were chemotherapy-naive experienced prostate-specific antigen decline ≥50% and ≥90%, respectively; median radiographic PFS was 3.7 months, and median OS was 28.1 months[1129].

Erlotinib

Assay findings association

EGFR
G724S

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[262,1130-1132] . For patients harboring co-occurring EGFR activating alterations, G724S was found to be associated with acquired resistance to first-generation EGFR TKIs in a case series[287], although 2 case studies reported SD to such inhibitors[288-289] . First-generation TKIs are therefore unlikely to benefit patients with G724S and concurrent activating EGFR mutations. Limited preclinical evidence suggests that G724S in the absence of another activating EGFR alteration may reduce sensitivity to erlotinib[285] and gefitinib[281].

SUPPORTING DATA

In the MyPathway Phase 2a basket study for advanced solid tumors, 1 of 9 patients with EGFR activating mutations responded to erlotinib monotherapy; the responding patient had urethral adenocarcinoma[1133]. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months[1134]. A Phase 2 trial of erlotinib in patients with metastatic prostate cancer reported clinical benefit in 40% of patients, though no decreases in PSA upon treatment were seen in any of 30 patients[1135]. Another Phase 2 trial of erlotinib in castration-resistant prostate cancer reported a clinical benefit in 31% of 22 patients and a strong decrease in PSA levels in 2 patients[1136].

Gefitinib

Assay findings association

EGFR
G724S

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[1132,1137-1142] , and responses have been reported for patients with EGFR-rearranged NSCLC[1143-1144] . For patients harboring co-occurring EGFR activating alterations, G724S was found to be associated with acquired resistance to first-generation EGFR TKIs in a case series[287], although 2 case studies reported SD to such inhibitors[288-289] . First-generation TKIs are therefore unlikely to benefit patients with G724S and concurrent activating EGFR mutations. Limited preclinical evidence suggests that G724S in the absence of another activating EGFR alteration may reduce sensitivity to erlotinib[285] and gefitinib[281].

SUPPORTING DATA

A Phase 2 trial of gefitinib in patients with hormone-naïve prostate cancer did not meet its primary objective in PSA stabilization or reduction[1145]. In patients with castration-resistant prostate cancer, the results of a Phase 2 trial of gefitinib as a single agent were not promising, with a response rate of just 2% and toxicities reported[1146]. A Phase 1/2 trial in 42 patients with non-metastatic prostate cancer of gefitinib with concurrent radiotherapy reported clinical activity and an overall survival rate of 87%[1147]. Another Phase 2 trial did not report much increased clinical activity upon addition of gefitinib to prednisone treatment in hormone-refractory prostate cancer[1148].

Niraparib

Assay findings association

BARD1
R406*

BRCA2
D946fs*14

BRIP1
splice site 918+1G>A - subclonal

CDK12
R1048*, N474fs*8 - subclonal

CHEK1
T226fs*14

FANCL
G119*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[85,245,1056], breast[175], endometrial[1057], and prostate cancer[174], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in ovarian and breast cancers[83-84,1149], loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib. On the basis of clinical evidence in ovarian cancer[70,245], FANCL loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in prostate[80,174,210,1058-1059], loss or inactivation of genes that are involved in homologous recombination repair may confer sensitivity to PARP inhibitors. CHEK1 inhibition has been associated with sensitivity to PARPi in preclinical studies[224,1060]. On the basis of preclinical evidence[71,74] and clinical evidence in ovarian cancer[70], BARD1 loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of limited clinical benefit in prostate[209-210,1062] and ovarian[1063] cancer, CDK12 inactivating alterations may confer sensitivity to PARP inhibitors.

SUPPORTING DATA

The Phase 2 GALAHAD study of niraparib for patients with metastatic castration-resistant prostate cancer who had progressed on at least 1 line of AR-targeted therapy in addition to at least 1 line of taxane chemotherapy reported an ORR of 34% (26/76) and a median radiographic PFS of 5.5 months for patients with biallelic BRCA1 or BRCA2 alterations[1150]. Patients in this trial with biallelic alterations in non-BRCA1/2 DNA repair genes experienced an 11% (5/47) ORR[1150].

Nivolumab

Assay findings association

CDK12
R1048*, N474fs*8 - subclonal

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved as a monotherapy in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, colorectal cancer (CRC), classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma or squamous cell carcinoma (ESCC). It is also approved in combination with chemotherapy to treat ESCC, in combination with cabozantinib to treat RCC, and in combination with relatlimab to treat melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of limited clinical evidence in prostate cancer, including multiple prostate-specific antigen (PSA) responses, CDK12 inactivating alterations may predict sensitivity to PD-1 inhibitors[194,1049-1050] . On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[3,6] , MSI-H status may predict sensitivity to nivolumab. On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] .

SUPPORTING DATA

Patients with CDK12-mutated metastatic castration-resistant prostate cancer (mCRPC) treated with nivolumab combined with the anti-CTLA-4 immunotherapy ipilimumab experienced a composite response rate of 14% (1/7) in the NEPTUNES trial[201] and a prostate-specific antigen (PSA) ≥50% decline in 14% (4/28) of patients in the IMPACT trial; unconfirmed PSA ≥30% decline was additionally observed in 21% (6/28) of patients[202]. PSA response rates of approximately 11-50% (2/19-2/4) were observed in retrospective studies of patients with CDK12-mutated metastatic prostate cancer treated with immune checkpoint inhibitors, which were predominantly anti-PD-1 monotherapies, such as nivolumab[194,198-200] . A Phase 2 study of nivolumab and ipilimumab combination therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) reported ORRs of 25% (8/32; 2 CRs) and 10% (3/30; 2 CRs) for chemotherapy-naive patients who had progressed on androgen deprivation therapy and patients who had progressed on chemotherapy, respectively[42]. Patients with tumor mutational burden (TMB) values above the study median achieved significantly better outcomes compared with patients with lower TMB values in the combined cohorts (ORR of 50% [9/18] vs. 5.3% [1/19], median PFS of 7.4 vs. 2.4 months)[42]. The CheckMate 9KD Phase 2 trial for patients with mCRPC reported ORRs of 37% (7/19; 1 CR, 6 PRs) and a median radiographic PFS of 8.2 months following combination treatment of nivolumab and docetaxel[1122]. Arm A2 of the same trial observed an ORR of 15% (6/39; all PRs) and median OS (mOS) of 20.2 months following combination treatment of nivolumab and rucaparib, with higher responses observed in a subset of patients with HRD+ tumors (ORR 25% [5/20]; all PRs, mOS of 22.7 months)[1151]. A Phase 1 study of nivolumab monotherapy did not report any objective responses for the 17 patients with genomically unselected CRPC[1152].

Nivolumab + Ipilimumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[37-38,1153] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment. On the basis of clinical data across solid tumors[3-5,1154-1158] , microsatellite instability high (MSI-H) status may predict sensitivity to combination nivolumab and ipilimumab.

SUPPORTING DATA

Preliminary results from a Phase 2 study of nivolumab and ipilimumab combination therapy in metastatic castration-resistant prostate cancer (mCRPC) reported ORRs of 25% (8/32, 2 CRs) and 10% (3/30, 2 CRs) for patients who were chemotherapy-naive and had progressed on androgen deprivation therapy and for patients who had progressed on chemotherapy, respectively[42]. Within the same trial, patients with post-chemotherapy mCRPC reported ORRs of 9-20% (4/43 and 8/41) for cohorts treated with nivolumab and ipilimumab regimens, 5% (1/22) for those receiving ipilimumab alone, and 12% (5/41) for cohorts receiving cabazitaxel; CRs were only observed in cohorts receiving the combination treatment[1159].

Retifanlimab

Assay findings association

CDK12
R1048*, N474fs*8 - subclonal

Microsatellite status
MSI-High

Tumor Mutational Burden
350 Muts/Mb

AREAS OF THERAPEUTIC USE

Retifanlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with Merkel cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[34-36,49,1048] , 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[34-35] . On the basis of limited clinical evidence in prostate cancer, including multiple prostate-specific antigen (PSA) responses, CDK12 inactivating alterations may predict sensitivity to PD-1 inhibitors[194,1049-1050] . On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[3,6-7,1080-1083,1160] , MSI-H status may predict sensitivity to retifanlimab.

SUPPORTING DATA

Clinical data on the efficacy of retifanlimab for the treatment of prostate cancer are limited (PubMed, Mar 2023). The efficacy of retifanlimab has been demonstrated in various treatment settings for multiple advanced solid tumors, including Merkel cell carcinoma[1161], anal squamous cell carcinoma (SCC)[1162], microsatellite instability-high or deficient MMR endometrial carcinoma[1160], glioblastoma[1163], soft tissue sarcoma[1164], and gastroesophageal adenocarcinoma[1165]. The Phase 2 POD1UM-201 trial of retifanlimab for patients with chemotherapy-naive advanced Merkel cell carcinoma reported an ORR of 51% (33/65; 11 CRs, 22 PRs), unreached median duration of response, and median PFS (mPFS) of 13.8 months[1161]. In the Phase 2 POD1UM-202 study for patients with previously treated advanced squamous carcinoma of the anal canal, retifanlimab elicited an ORR of 14% (13/94; 1 CR, 12 PRs), mPFS of 2.3 months, and median OS of 10.1 months, with responses observed regardless of PD-L1 expression[1162]. In the Phase 2 POD1UM-203 trial for multiple tumor types, retifanlimab yielded an ORR of 35% (8/23) and mPFS of 4.4 months for patients with treatment-naive metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (TPS ≥50%), an ORR of 40% (14/35) and mPFS of 3.6 months for patients with unresectable or metastatic melanoma, an ORR of 38% (11/29) and mPFS of 5.7 months for patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma with PD-L1 expression (CPS ≥10%), and an ORR of 24% (8/34; 1 CR, 7 PRs) and mPFS of 5.4 months for patients with treatment-naive advanced clear cell renal cell carcinoma (RCC)[1166].

Talazoparib

Assay findings association

BARD1
R406*

BRCA2
D946fs*14

BRIP1
splice site 918+1G>A - subclonal

CDK12
R1048*, N474fs*8 - subclonal

CHEK1
T226fs*14

FANCL
G119*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[85,245,1056], breast[175], endometrial[1057], and prostate cancer[174], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in ovarian cancer[70,245], FANCL loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of clinical evidence in prostate[80,174,210,1058-1059], loss or inactivation of genes that are involved in homologous recombination repair may confer sensitivity to PARP inhibitors. CHEK1 inhibition has been associated with sensitivity to PARPi in preclinical studies[224,1060]. On the basis of preclinical evidence[71,74] and clinical evidence in ovarian cancer[70], BARD1 loss or inactivation may confer sensitivity to PARP inhibitors. On the basis of limited clinical benefit in prostate[209-210,1062] and ovarian[1063] cancer, CDK12 inactivating alterations may confer sensitivity to PARP inhibitors. On the basis of strong clinical data in breast cancer[1167-1169] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[1170-1173], loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

The Phase 3 TALAPRO-2 trial of talazoparib plus enzalutamide as a first-line treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) reported a significantly improved radiographic PFS (rPFS) (NR vs. 21.9 months, HR=0.63) and ORR (62% vs. 44%), but OS (36.4 months vs. NR, HR=0.89) was not improved compared with placebo plus enzalutamide; greater rPFS benefit was observed among patients with homologous recombination repair (HRR) mutations (27.9 vs. 16.4 months, HR=0.46) than those without HRR mutations or of unknown HRR status (NR vs. 22.5 months, HR=0.70)[1174]. The Phase 2 TALAPRO-1 trial of talazoparib monotherapy for patients with docetaxel-treated mCRPC harboring alterations in DNA repair genes reported a study-wide ORR of 30% with median rPFS of 5.6 months, with an ORR of 46% (28/61) and rPFS of 11.2 months for patients with BRCA1/2 mutations[1175]. A retrospective subgroup analysis found no association between antitumor activity and germline HRR alterations (gHRRm) (ORR: 31% [5/16] vs. 26% [14/54] in patients assigned male at birth with vs. without gHRRm, respectively); ORRs were also similar for patients with gHRRm or with only somatic HRRm (25% [10/40] vs. 19% [4/21], respectively, [p=0.7528])[1176].

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.

Electronically signed by Brennan Decker, M.D., Ph.D. | 04 June 2023
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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

BIOMARKER

Microsatellite status

RESULT

MSI-High

RATIONALE

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

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT04100018

PHASE 3

A Study of Nivolumab or Placebo in Combination With Docetaxel in Men With Advanced Castration-resistant Prostate Cancer

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Niaosng (Taiwan), Hangzhou (China), Shanghai (China), Nanchang (China), Nanchang Shi (China), Hong Kong (Hong Kong)

NCT02628067

PHASE 2

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

TARGETS
PD-1

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

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04446117

PHASE 3

Study of Cabozantinib in Combination With Atezolizumab Versus Second NHT in Subjects With mCRPC

TARGETS
AR, PD-L1, MET, ROS1, RET, VEGFRs, CYP17

LOCATIONS: Taoyuan (Taiwan), Taichung (Taiwan), Taichung City (Taiwan), Kaohsiung (Taiwan), Taipei city (Taiwan), Tainan City (Taiwan), Tainan (Taiwan), Hwasun (Korea, Republic of), Gwangju (Korea, Republic of), Fukuoka (Japan)

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

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

NCT03821935

PHASE 1

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

TARGETS
PD-1, GARP

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

NCT04282018

PHASE 1/2

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

TARGETS
PI3K-delta, PD-1, BTK

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

BIOMARKER

Tumor Mutational Burden

RESULT

350 Muts/Mb

RATIONALE

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

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT04100018

PHASE 3

A Study of Nivolumab or Placebo in Combination With Docetaxel in Men With Advanced Castration-resistant Prostate Cancer

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Niaosng (Taiwan), Hangzhou (China), Shanghai (China), Nanchang (China), Nanchang Shi (China), Hong Kong (Hong Kong)

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04589845

PHASE 2

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

NCT04446117

PHASE 3

Study of Cabozantinib in Combination With Atezolizumab Versus Second NHT in Subjects With mCRPC

TARGETS
AR, PD-L1, MET, ROS1, RET, VEGFRs, CYP17

LOCATIONS: Taoyuan (Taiwan), Taichung (Taiwan), Taichung City (Taiwan), Kaohsiung (Taiwan), Taipei city (Taiwan), Tainan City (Taiwan), Tainan (Taiwan), Hwasun (Korea, Republic of), Gwangju (Korea, Republic of), Fukuoka (Japan)

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

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

NCT03821935

PHASE 1

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

TARGETS
PD-1, GARP

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

NCT04215978

PHASE 1

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

TARGETS
PD-1, OX40

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

GENE
APC

ALTERATION
R876*

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnamsi Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seodaemun (Korea, Republic of), Seoul (Korea, Republic of), Jongno-gu (Korea, Republic of), Osakasayama (Japan)

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), California, Arizona, Minnesota

GENE
BARD1

ALTERATION
R406*

RATIONALE
Tumors with BARD1 inactivating mutation or loss may be sensitive to PARP inhibitors.

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT05489211

PHASE 2

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

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT05376722

PHASE 2

A Study of Pamiparib Combined With Abiraterone Acetate in Neoadjuvant Treatment of Prostate Cancer

TARGETS
CYP17

LOCATIONS: Nanjing (China)

GENE
BRCA2

ALTERATION
D946fs*14

RATIONALE
BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors or to ATR inhibitors.

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT05489211

PHASE 2

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

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05457257

PHASE 4

Clinical Study to Assess the Efficacy and Safety of Olaparib in Chinese Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment With a New Hormonal Agent and Have BRCA1/2 Mutations

TARGETS
CYP17, PARP, AR

LOCATIONS: Fuzhou (China), Ningbo (China), Hangzhou (China), Jiaxing (China), Shanghai (China), Nanchang (China), Suzhou (China), Wuxi (China), Nantong (China), Hefei (China)

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, 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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

GENE
BRIP1

ALTERATION
splice site 918+1G>A - subclonal

RATIONALE
BRIP1 inactivation may predict sensitivity to inhibitors of other DNA repair pathways, including inhibitors of PARP.

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT05489211

PHASE 2

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

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT05376722

PHASE 2

A Study of Pamiparib Combined With Abiraterone Acetate in Neoadjuvant Treatment of Prostate Cancer

TARGETS
CYP17

LOCATIONS: Nanjing (China)

GENE
CDK12

ALTERATION
R1048*, N474fs*8 - subclonal

RATIONALE
Preclinical and clinical data suggest that tumors with CDK12 mutation or loss may be sensitive to PARP inhibitors. Preclinical and limited clinical evidence indicate that CDK12 inactivation in prostate cancer may predict benefit from anti-PD-1 immune checkpoint inhibitors.

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT04100018

PHASE 3

A Study of Nivolumab or Placebo in Combination With Docetaxel in Men With Advanced Castration-resistant Prostate Cancer

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Niaosng (Taiwan), Hangzhou (China), Shanghai (China), Nanchang (China), Nanchang Shi (China), Hong Kong (Hong Kong)

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT05489211

PHASE 2

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

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

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT03821935

PHASE 1

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

TARGETS
PD-1, GARP

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

GENE
CHEK1

ALTERATION
T226fs*14

RATIONALE
On the basis of limited clinical benefit in prostate cancer, CHEK1 alterations may confer sensitivity to PARP inhibitors.

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT05489211

PHASE 2

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

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT05376722

PHASE 2

A Study of Pamiparib Combined With Abiraterone Acetate in Neoadjuvant Treatment of Prostate Cancer

TARGETS
CYP17

LOCATIONS: Nanjing (China)

GENE
EGFR

ALTERATION
G724S

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies. On the basis of clinical data, EGFR G724S may reduce response to erlotinib, gefitinib, and osimertinib, as well as other third-generation EGFR TKIs.

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04946968

PHASE 2

Phase-2 Dacomitinib Study on Patients With EGFR-Driven Advanced Solid Tumours With Low EGFR-AS1 lncRNA Expr or Other Novel Emerging Biomarkers

TARGETS
ERBB4, EGFR, ERBB2

LOCATIONS: Singapore (Singapore)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT04670679

PHASE 1

A Dose Escalation/Expansion Study of ERAS-601 in Patients With Advanced or Metastatic Solid Tumors

TARGETS
SHP2, EGFR

LOCATIONS: Perth (Australia), Melbourne (Australia), Nevada, California, Missouri, Texas, Massachusetts, New York, Pennsylvania, Tennessee

GENE
FANCL

ALTERATION
G119*

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

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT05489211

PHASE 2

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

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

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

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT05376722

PHASE 2

A Study of Pamiparib Combined With Abiraterone Acetate in Neoadjuvant Treatment of Prostate Cancer

TARGETS
CYP17

LOCATIONS: Nanjing (China)

GENE
PIK3CA

ALTERATION
E970K

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.

NCT05348577

PHASE 3

Study of Capivasertib + Docetaxel vs Placebo + Docetaxel as Treatment for Metastatic Castration Resistant Prostate Cancer (mCRPC)

TARGETS
AKTs

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Ningbo (China), Hangzhou (China), Jiaxing (China), Shanghai (China), Nanchang (China), Shenzhen (China)

NCT04589845

PHASE 2

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (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)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03385655

PHASE 2

Prostate Cancer Biomarker Enrichment and Treatment Selection

TARGETS
AR, WEE1, PD-L1, AKTs, PLK4, CTLA-4, MET

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

GENE
PTEN

ALTERATION
P246L, K267fs*9, R173C

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.

NCT05348577

PHASE 3

Study of Capivasertib + Docetaxel vs Placebo + Docetaxel as Treatment for Metastatic Castration Resistant Prostate Cancer (mCRPC)

TARGETS
AKTs

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Ningbo (China), Hangzhou (China), Jiaxing (China), Shanghai (China), Nanchang (China), Shenzhen (China)

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), North Ryde (Australia), Moscow (Russian Federation), Kiev (Ukraine), Espoo (Finland), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT04434482

PHASE 1

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

TARGETS
PARP

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

NCT05405439

PHASE 1/2

To Evaluate the Efficacy of TQB3823 Combined With Abiraterone and Prednisone in Metastatic Castration-resistant Prostate Cancer Patientsprednisone Acetate Tablets in Patients With Metastatic Castration-resistant Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Wenzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Qingyuan (China), Changsha (China), Jinan (China), Nanning (China), Chongqing (China), Xi'an (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

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

NCT05376722

PHASE 2

A Study of Pamiparib Combined With Abiraterone Acetate in Neoadjuvant Treatment of Prostate Cancer

TARGETS
CYP17

LOCATIONS: Nanjing (China)

NCT05406999

PHASE 2

Neoadjuvant Intense Endocrine Therapy for High Risk and Locally Advanced Prostate Cancer

TARGETS
PARP, CYP17

LOCATIONS: Nanjing (China)

NCT05021367

PHASE 1

A Clinical Study of TQB3823 in Patients With Advanced Malignant Tumor

TARGETS
PARP

LOCATIONS: Guangzhou (China)

GENE
RNF43

ALTERATION
G659fs*41, H683fs*17

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT02521844

PHASE 1

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

TARGETS
PORCN

LOCATIONS: Singapore (Singapore), Colorado, Texas, North Carolina

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

GENE
TSC2

ALTERATION
R57H

RATIONALE
Inactivating TSC2 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, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT05103358

PHASE 2

Phase 2 Basket Trial of Nab-sirolimus in Patients With Malignant Solid Tumors With Pathogenic Alterations in TSC1 or TSC2 Genes (PRECISION 1)

TARGETS
mTOR

LOCATIONS: Hawaii, Washington, California, Utah

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
CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT05661461

PHASE 1

Dose-escalation Study to Assess Safety and Pharmacokinetics of Nab-Sirolimus in Patients With Locally Advanced or Metastatic Solid Tumors and Moderate Liver Impairment

TARGETS
mTOR

LOCATIONS: Utah, Texas

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

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
NM_005157.4: c.3001G>A (p.A1001T)
chr9:133760678 and
NM_005157.4: c.443G>A (p.S148N)
chr9:133730377

ALK
NM_004304.4: c.4690G>A (p.A1564T)
chr2:29416263 and
NM_004304.4: c.4306C>T (p.R1436C)
chr2:29416647

AMER1 (FAM123B OR WTX)
NM_152424.3: c.1828G>A (p.A610T)
chrX:63411339 and
NM_152424.3: c.1732C>T (p.L578F)
chrX:63411435

APC
NM_000038.4: c.2876C>T (p.S959F)
chr5:112174167 and
NM_000038.4: c.5465_5467delinsACG (p.V1822_F1823delinsDV)
chr5:112176756-112176758

AR
NM_000044.2: c.791G>A (p.R264Q)
chrX:66765779

ARAF
NM_001654.3: c.229G>T (p.A77S)
chrX:47424224 and
NM_001654.3: c.521G>A (p.R174H)
chrX:47424713

ARFRP1
NM_003224.3: c.2T>A (p.M1?)
chr20:62338442

ARID1A
NM_006015.4: c.4973G>A (p.R1658Q)
chr1:27101691, NM_006015.4: c.6694C>T (p.R2232W)
chr1:27107083 and
NM_006015.4: c.3869C>T (p.T1290M)
chr1:27100073

ASXL1
NM_015338.5: c.3442C>T (p.R1148C)
chr20:31023957

ATM
NM_000051.3: c.1411A>G (p.N471D)
chr11:108121603,
NM_000051.3: c.7375C>T (p.R2459C)
chr11:108201008,
NM_000051.3: c.7858G>A (p.V2620I)
chr11:108203558 and
NM_000051.3: c.2746G>A (p.V916M)
chr11:108139244

AURKA
NM_003600.2: c.251T>C (p.V84A)
chr20:54961381

BARD1
NM_000465.2: c.268G>A (p.A90T)
chr2:215657117

BCL6
NM_001706.4: c.996G>T (p.Q332H)
chr3:187447197

BRCA2
NM_000059.3: c.2918C>T (p.S973L)
chr13:32911410 and
NM_000059.3: c.7591G>A (p.V2531I)
chr13:32930720

CCND1
NM_053056.2: c.733C>T (p.R245W)
chr11:69465895

CCND2
NM_001759.3: c.445T>C (p.W149R)
chr12:4387959

CCNE1
NM_001238.1: c.236A>G (p.D79G)
chr19:30308099

CD22
NM_001771.3: c.2029G>A (p.V677I)
chr19:35832862

CD79B
NM_000626.2: c.338G>A (p.R113Q)
chr17:62007526

CDK12
NM_016507.2: c.2456A>T (p.D819V)
chr17:37657539 and
NM_016507.2: c.1753C>T (p.P585S)
chr17:37627838

CDK8
NM_001260.1: c.1328G>A (p.S443N)
chr13:26978151

CDKN2A/B
NM_004936.3: c.20G>A (p.G7D)
chr9:22008933

CHEK1
NM_001274.4: c.587T>C (p.I196T)
chr11:125503220

CIC
NM_015125.4: c.1852G>A (p.A618T)
chr19:42794772

CREBBP
NM_004380.2: c.6431C>T (p.A2144V)
chr16:3778617,
NM_004380.2: c.2896G>T (p.A966S)
chr16:3819339 and
NM_004380.2: c.1184T>C (p.M395T)
chr16:3843419

CSF3R
NM_156039.3: c.881T>C (p.L294P)
chr1:36937955

CTCF
NM_006565.3: c.528G>T (p.E176D)
chr16:67645263,
NM_006565.3: c.187A>G (p.M63V)
chr16:67644922 and
NM_006565.3: c.752C>T (p.P251L)
chr16:67645487

CTNNA1
NM_001903.2: c.1486C>T (p.R496C)
chr5:138253527

CTNNB1
NM_001904.3: c.932G>T (p.S311I)
chr3:41267348

CXCR4
NM_001008540.1: c.1021C>T (p.H341Y)
chr2:136872489

CYP17A1
NM_000102.3: c.213G>T (p.K71N)
chr10:104596906

DAXX
NM_001350.4: c.1986G>T (p.K662N)
chr6:33286951

DDR1
NM_001954.4: c.1756dup (p.E586Gfs*6)
chr6:30864636,
NM_001954.4: c.474del (p.M159Wfs*16)
chr6:30858800-30858801,
NM_001954.4: c.178C>T (p.R60C)
chr6:30856777 and
NM_001954.4: c.1514-1G>A (p.?)
chr6:30864397

DIS3
NM_001128226.1: c.29del (p.K10Rfs*7)
chr13:73355941-73355942 and NM_001128226.1: c.892C>T (p.R298*)
chr13:73349354

DOT1L
NM_032482.2: c.4504C>T (p.P1502S)
chr19:2227024,
NM_032482.2: c.1237C>T (p.R413C)
chr19:2210740 and
NM_032482.2: c.2191T>C (p.S731P)
chr19:2216547

EGFR
NM_005228.3: c.162G>A (p.M54I)
chr7:55210052 and
NM_005228.3: c.2011C>T (p.R671C)
chr7:55240767

EP300
NM_001429.3: c.6413C>T (p.A2138V)
chr22:41574128,
NM_001429.3: c.4383G>T (p.K1461N)
chr22:41566506,
NM_001429.3: c.4411C>T (p.L1471F)
chr22:41566534 and
NM_001429.3: c.7177C>G (p.L2393V)
chr22:41574892

EPHA3
NM_005233.4: c.962C>T (p.A321V)
chr3:89390213,
NM_005233.4: c.860G>A (p.C287Y)
chr3:89390111 and
NM_005233.4: c.1777C>A (p.L593I)
chr3:89462305

EPHB1
NM_004441.4: c.2092G>A (p.E698K)
chr3:134911627

EPHB4
NM_004444.4: c.898G>A (p.A300T)
chr7:100417829,
NM_004444.4: c.2918A>C (p.K973T)
chr7:100401129 and
NM_004444.4: c.718C>T (p.R240C)
chr7:100419983

ERBB4
NM_005235.2: c.3749G>A (p.R1250Q)
chr2:212248518

ERCC4
NM_005236.2: c.341T>C (p.L114P)
chr16:14016021

ERG
NM_182918.3: c.1099C>T (p.R367C)
chr21:39755666

FANCA
NM_000135.2: c.1247C>T (p.A416V)
chr16:89857923

FANCG
NM_004629.1: c.1235A>G (p.D412G)
chr9:35075660

FANCL
NM_018062.3: c.203G>A (p.R68Q)
chr2:58456962

FGF10
NM_004465.1: c.82T>C (p.F28L)
chr5:44388703 and
NM_004465.1: c.101C>T (p.P34L)
chr5:44388684

FGF4
NM_002007.2: c.428G>T (p.G143V)
chr11:69588808

FGFR2
NM_000141.4: c.108A>C (p.E36D)
chr10:123353224

FGFR3
NM_000142.3: c.1630G>A (p.A544T)
chr4:1807381, NM_000142.3: c.1697_1715dup (p.P573Sfs*98)
chr4:1807527 and
NM_000142.3: c.587G>A (p.R196H)
chr4:1803235

FGFR4
NM_213647.3: c.1094C>T (p.A365V)
chr5:176520175 and
NM_213647.3: c.1793G>A (p.R598Q)
chr5:176522696

FLCN
NM_144997.5: c.1327G>A (p.A443T)
chr17:17118604

FLT1
NM_002019.4: c.166del (p.E56Kfs*12)
chr13:29041261-29041262 and NM_002019.4: c.3695del (p.L1232Yfs*24)
chr13:28883004-28883005

FLT3
NM_004119.2: c.2416T>C (p.S806P)
chr13:28597489,
NM_004119.2: c.807G>A (p.W269*)
chr13:28623847 and
NM_004119.2: c.2542-1G>A (p.?)
chr13:28589839

GABRA6
NM_000811.2: c.825del (p.F275Lfs*7)
chr5:161117353-161117354,
NM_000811.2: c.340C>T (p.P114S)
chr5:161116069 and
NM_000811.2: c.248dup (p.R84Pfs*6)
chr5:161115970

GATA3
NM_001002295.1: c.373G>A (p.G125S)
chr10:8100399

GATA6
NM_005257.3: c.493G>A (p.A165T)
chr18:19751598 and
NM_005257.3: c.323G>T (p.S108I)
chr18:19751428

GNA11
NM_002067.2: c.752G>A (p.S251N)
chr19:3119220

GNAS
NM_080425.2: c.317C>T (p.A106V)
chr20:57428637,
NM_016592.2: c.505C>T (p.R169*)
chr20:57415666 and
NM_000516.4: c.970+1G>A (p.?)
chr20:57485137

GRM3
NM_000840.2: c.691G>A (p.E231K)
chr7:86415799 and
NM_000840.2: c.868C>T (p.R290C)
chr7:86415976

GSK3B
NM_002093.3: c.316C>T (p.H106Y)
chr3:119666165

HDAC1
NM_004964.2: c.1354G>T (p.D452Y)
chr1:32797825

HNF1A
NM_000545.4: c.864delinsCC (p.G292Rfs*25)
chr12:121432117 and
NM_000545.4: c.775G>A (p.V259I)
chr12:121432028

INPP4B
NM_003866.2: c.2337A>C (p.E779D)
chr4:143029283 and
NM_003866.2: c.1058G>A (p.S353N)
chr4:143129592

IRF2
NM_002199.3: c.745C>T (p.R249W)
chr4:185310217

IRF4
NM_002460.3: c.946G>A (p.V316I)
chr6:401624

IRS2
NM_003749.2: c.1826C>T (p.A609V)
chr13:110436575,
NM_003749.2: c.2321C>T (p.A774V)
chr13:110436080,
NM_003749.2: c.1658G>A (p.G553D)
chr13:110436743,
NM_003749.2: c.3626C>T (p.P1209L)
chr13:110434775 and
NM_003749.2: c.2591C>A (p.P864H)
chr13:110435810

JAK1
NM_002227.2: c.521G>A (p.R174Q)
chr1:65335120

JAK2
NM_004972.3: c.3245dup (p.L1082Ffs*4)
chr9:5126396

JAK3
NM_000215.3: c.1820C>T (p.A607V)
chr19:17946827 and
NM_000215.3: c.309-1G>T (p.?)
chr19:17954301

KDM5A
NM_001042603.1: c.3597del (p.G1200Dfs*9)
chr12:416952-416953,
NM_001042603.1: c.473del (p.L158*)
chr12:475163-475164,
NM_001042603.1: c.2947A>G (p.N983D)
chr12:422311 and
NM_001042603.1: c.3091C>T (p.R1031C)
chr12:420176

KEAP1
NM_012289.3: c.1510A>G (p.N504D)
chr19:10600345

KEL
NM_000420.2: c.538C>T (p.R180C)
chr7:142655048

KMT2A (MLL)
NM_005933.3: c.9938C>T (p.A3313V)
chr11:118376554 and
NM_005933.3: c.11456G>A (p.R3819H)
chr11:118391552

KMT2D (MLL2)
NM_003482.4: c.592G>A (p.A198T)
chr12:49447842,
NM_003482.4: c.2120C>T (p.A707V)
chr12:49445346,
NM_003482.4: c.6139A>G (p.K2047E)
chr12:49435744 and
NM_003482.4: c.7254G>C (p.Q2418H)
chr12:49434299

LTK
NM_002344.5: c.1808G>T (p.R603M)
chr15:41797618

MAF
NM_005360.4: c.905C>T (p.A302V)
chr16:79632895

MAPK1
NM_002745.4: c.802C>T (p.P268S)
chr22:22142600

MDM2
NM_002392.3: c.1328C>A (p.P443H)
chr12:69233463

MEF2B
NM_001145785.1: c.407C>T (p.A136V)
chr19:19257979,
NM_001145785.1: c.861del (p.A288Pfs*116)
chr19:19257101-19257102 and
NM_001145785.1: c.944dup (p.V316Sfs*6)
chr19:19256768

MERTK
NM_006343.2: c.2186G>A (p.C729Y)
chr2:112777096,
NM_006343.2: c.1714G>A (p.E572K)
chr2:112760692 and
NM_006343.2: c.2782C>T (p.R928W)
chr2:112786223

MET
NM_000245.2: c.1475T>C (p.V492A)
chr7:116380086

MKNK1
NM_003684.4: c.103C>T (p.R35W)
chr1:47048933

MST1R
NM_002447.2: c.464T>C (p.V155A)
chr3:49940579

MTAP
NM_002451.3: c.362C>A (p.P121H)
chr9:21837921

MTOR
NM_004958.3: c.2095G>A (p.A699T)
chr1:11298013, NM_004958.3: c.607C>T (p.Q203*)
chr1:11316147 and
NM_004958.3: c.3781A>G (p.S1261G)
chr1:11269389

MYC
NM_002467.4: c.650G>A (p.S217N)
chr8:128751113

MYCL (MYCL1)
NM_005376.4: c.341G>A (p.R114K)
chr1:40366856

MYCN
NM_005378.4: c.511G>A (p.A171T)
chr2:16082697,
NM_005378.4: c.551C>T (p.A184V)
chr2:16082737 and
NM_005378.4: c.754C>T (p.L252F)
chr2:16082940

NBN
NM_002485.4: c.452T>C (p.V151A)
chr8:90992990 and
NM_002485.4: c.1249G>A (p.V417I)
chr8:90967659

NF1
NM_001042492.2: c.8498A>G (p.N2833S)
chr17:29701151,
NM_001042492.2: c.197A>G (p.N66S)
chr17:29483137 and
NM_001042492.2: c.467G>A (p.R156H)
chr17:29490382

NOTCH1
NM_017617.3: c.6787C>T (p.R2263W)
chr9:139391404

NOTCH2
NM_024408.3: c.1105G>A (p.A369T)
chr1:120512137 and
NM_024408.3: c.1043C>T (p.T348I)
chr1:120512199

NOTCH3
NM_000435.2: c.1739A>G (p.E580G)
chr19:15298017,
NM_000435.2: c.2413C>A (p.P805T)
chr19:15295259,
NM_000435.2: c.3725G>A (p.R1242H)
chr19:15289746 and
NM_000435.2: c.4619G>A (p.R1540H)
chr19:15284996

NSD2 (WHSC1 OR MMSET)
NM_133335.3: c.1862C>T (p.A621V)
chr4:1941486 and
NM_133335.3: c.1601A>G (p.D534G)
chr4:1936916

NTRK1
NM_002529.3: c.922C>T (p.Q308*)
chr1:156843496

NTRK2
NM_006180.3: c.1264G>A (p.V422I)
chr9:87359956

NTRK3
NM_002530.2: c.2470C>T (p.L824F)
chr15:88420174

PARP1
NM_001618.3: c.989G>A (p.R330Q)
chr1:226573227 and
NM_001618.3: c.1063C>T (p.R355C)
chr1:226570833

PARP2
NM_005484.3: c.1112C>T (p.P371L)
chr14:20824162 and
NM_005484.3: c.1320C>A (p.S440R)
chr14:20824800

PDCD1 (PD-1)
NM_005018.2: c.852C>A (p.C284*)
chr2:242793225 and
NM_005018.2: c.755T>C (p.V252A)
chr2:242793322

PDGFRA
NM_006206.4: c.1891C>T (p.P631S)
chr4:55143659

PDGFRB
NM_002609.3: c.2278G>A (p.D760N)
chr5:149501509 and
NM_002609.3: c.1811G>A (p.R604H)
chr5:149504391

PIK3C2G
NM_004570.4: c.310G>A (p.A104T)
chr12:18435325 and
NM_004570.4: c.1523T>C (p.V508A)
chr12:18499668

PIK3R1
NM_181523.3: c.1469C>T (p.T490I)
chr5:67590407

PIM1
NM_002648.3: c.480C>A (p.N160K)
chr6:37139140

POLE
NM_006231.2: c.3593C>T (p.A1198V)
chr12:133226465,
NM_006231.2: c.2683G>A (p.A895T)
chr12:133240613,
NM_006231.2: c.2091dup (p.F699Vfs*11)
chr12:133245023,
NM_006231.2: c.4472A>G (p.H1491R)
chr12:133219889 and
NM_006231.2: c.1372T>C (p.Y458H)
chr12:133249851

PPP2R1A
NM_014225.5: c.313C>T (p.R105W)
chr19:52714555

PRKN (PARK2)
NM_004562.2: c.1381C>A (p.H461N)
chr6:161771148

PTCH1
NM_000264.3: c.1715C>T (p.A572V)
chr9:98238329

PTPRO
NM_030667.1: c.1544C>A (p.P515H)
chr12:15668511

RAD51B
NM_133509.3: c.769A>C (p.N257H)
chr14:68758613

RAD54L
NM_003579.3: c.296G>A (p.G99D)
chr1:46725660 and
NM_003579.3: c.785G>A (p.R262H)
chr1:46726951

RAF1
NM_002880.3: c.61G>A (p.V21M)
chr3:12660160

RARA
NM_000964.3: c.310G>A (p.A104T)
chr17:38504699

RET
NM_020975.4: c.1538C>T (p.A513V)
chr10:43607562

RICTOR
NM_152756.3: c.2974G>A (p.A992T)
chr5:38952451

RNF43
NM_017763.4: c.2195G>A (p.R732H)
chr17:56434942 and
NM_017763.4: c.1982C>T (p.S661F)
chr17:56435155

ROS1
NM_002944.2: c.4487A>G (p.D1496G)
chr6:117665260

RPTOR
NM_020761.2: c.1568C>T (p.A523V)
chr17:78854273

SETD2
NM_014159.6: c.4205G>A (p.G1402E)
chr3:47161921, NM_014159.6: c.1666A>G (p.K556E)
chr3:47164460,
NM_014159.6: c.1202G>A (p.R401Q)
chr3:47164924, NM_014159.6: c.209G>A (p.R70Q)
chr3:47165917 and
NM_014159.6: c.2848C>T (p.R950C)
chr3:47163278

SF3B1
NM_012433.2: c.2993A>G (p.K998R)
chr2:198264799

SMARCA4
NM_003072.3: c.145C>T (p.P49S)
chr19:11094972

SMO
NM_005631.4: c.586C>T (p.P196S)
chr7:128845092 and
NM_005631.4: c.782G>A (p.R261H)
chr7:128845485

SPEN
NM_015001.2: c.8476G>T (p.G2826C)
chr1:16261211 and
NM_015001.2: c.3065T>G (p.V1022G)
chr1:16255800

SRC
NM_005417.3: c.248C>T (p.A83V)
chr20:36012804 and
NM_005417.3: c.1163G>A (p.R388Q)
chr20:36030884

SYK
NM_003177.5: c.1108C>A (p.L370M)
chr9:93637058

TBX3
NM_016569.3: c.694G>A (p.G232R)
chr12:115117741

TEK
NM_000459.3: c.2744G>A (p.R915H)
chr9:27212762

TENT5C (FAM46C)
NM_017709.3: c.110G>A (p.G37E)
chr1:118165600

TET2
NM_001127208.2: c.2932C>T (p.H978Y)
chr4:106158031,
NM_001127208.2: c.4909C>A (p.L1637I)
chr4:106196576,
NM_001127208.2: c.3437C>A (p.P1146H)
chr4:106162523 and
NM_001127208.2: c.1088C>A (p.P363H)
chr4:106156187

TGFBR2
NM_003242.5: c.61G>A (p.A21T)
chr3:30648436,
NM_003242.5: c.383del (p.K128Sfs*35)
chr3:30691871-30691872 and
NM_003242.5: c.1484G>A (p.R495Q)
chr3:30729963

TIPARP
NM_015508.4: c.322T>C (p.S108P)
chr3:156395808 and
NM_015508.4: c.1219T>A (p.S407T)
chr3:156413786

TSC1
NM_000368.4: c.1837C>T (p.P613S)
chr9:135781128

TSC2
NM_000548.3: c.4370G>A (p.R1457Q)
chr16:2134593 and
NM_000548.3: c.1384C>T (p.R462C)
chr16:2112995

WT1
NM_024426.4: c.680G>A (p.S227N)
chr11:32450132

XPO1
NM_003400.3: c.1608_1610del (p.N536del)
chr2:61719572-61719575

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.9.0

The median exon coverage for this sample is 874x

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