FOUNDATIONONE®CDx

PATIENT
Chen, Yueh-E

TUMOR TYPE
Bladder urothelial (transitional cell) carcinoma

COUNTRY CODE
TW

REPORT DATE
17 Mar 2022

ORDERED TEST #
ORD-1318270-01

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 Bladder urothelial (transitional cell) carcinoma
NAME Chen, Yueh-E
DATE OF BIRTH 27 September 1957
SEX Female
MEDICAL RECORD # 42050191

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 Bladder
SPECIMEN ID S110-73920A (PF22034)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 13 December 2021
SPECIMEN RECEIVED 09 March 2022

Biomarker Findings

Tumor Mutational Burden - 11 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

FGFR3 S249C
ERBB2 S310F
ARID1A Q1537*, S1930*
MTAP loss
TSC1 Q527*
CDKN2A/B CDKN2A loss, CDKN2B loss
KDM6A Q147*
LYN E241D
TERT promoter -124C>T

1 Disease relevant genes with no reportable alterations: ***FGFR2***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Avelumab** (p. 11), **Pembrolizumab** (p. 14), **Atezolizumab** (p. 11), **Erdafitinib** (p. 12), **Nivolumab** (p. 13)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 21)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 11 Muts/Mb	Avelumab	1	Cemiplimab
	Pembrolizumab	1	Durvalumab
	Atezolizumab	2A	Nivolumab + Ipilimumab
	Nivolumab	2A	
	Dostarlimab		
10 Trials see p. 21			
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section		

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR3 - S249C	Erdafitinib 2A	Infigratinib
10 Trials see p. 27		
ERBB2 - S310F	none	Ado-trastuzumab emtansine
		Fam-trastuzumab deruxtecan
		Lapatinib
		Neratinib
		Trastuzumab
10 Trials see p. 25		Trastuzumab + Pertuzumab
ARID1A - Q1537*, S1930*	none	none
10 Trials see p. 23		
MTAP - loss	none	none
1 Trial see p. 29		
TSC1 - Q527*	none	none
10 Trials see p. 30		

2A *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

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BIOMARKER

Tumor Mutational Burden

RESULT
11 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. In multiple studies of immune checkpoint inhibitors in urothelial carcinoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-L1[1,11-15] and anti-PD-1 immunotherapeutic agents[16-17] . For patients with metastatic urothelial carcinoma treated with the PD-L1 inhibitor atezolizumab, those with a significantly increased mutational load (9.7 Muts/Mb or greater by this assay or others) were associated with response and longer OS compared with those with lower TMB[1,11-13]. Similarly, in a study of pembrolizumab in muscle invasive bladder cancer, the median TMB in responders was 12.3 Muts/Mb, versus 7.0 Muts/Mb in nonresponding patients[17]. The PD-1 inhibitor nivolumab led to increased ORR, PFS, and OS for patients with a TMB of 167 missense mutations/tumor or higher (~ equivalency = 9 Muts/Mb or higher as measured by this assay) compared with those harboring lower TMB in a study of metastatic urothelial cancer[16].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (muts/Mb)[18]. One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers[19]. For patients with metastatic urothelial carcinoma receiving atezolizumab, however, higher median mutation load has been reported to be significantly associated with improved PFS and OS[11-12,20].

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[21-22] and cigarette smoke in lung cancer[23-24], treatment with temozolomide-based chemotherapy in glioma[25-26], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[27-31], and microsatellite instability (MSI)[27,30-31]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in urothelial carcinoma[1,11-15,32].

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[33-35], including approved therapies nivolumab and pembrolizumab[36]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[37].

FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas[38-39]; MSI-H has also been reported in multiple case studies of upper urinary tract urothelial carcinoma[40]. MSI, as determined through loss of MSH2 or MSH6 protein expression, correlated with non-invasive, well-differentiated bladder tumors and favorable overall survival[38].

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[41]. 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[41-43]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[44-46]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[41,43,45-46].

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GENE
FGFR3

ALTERATION
S249C

TRANSCRIPT ID
NM_000142

CODING SEQUENCE EFFECT
746C>G

VARIANT ALLELE FREQUENCY (% VAF)
58.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR3 may predict sensitivity to selective FGFR kinase inhibitors, including erdafitinib[47-49], pemigatinib[50], infigratinib[51-52], rogaratinib[53], Debio 1347[54-55], and derazantinib[56]; multikinase inhibitors such as pazopanib[57-58] and ponatinib[59-60]; and vofatamab, an antibody targeting FGFR3[61-63] . A study of the tumor immune microenvironment in urothelial bladder cancer found enhanced FGFR3 pathway activation in non-T-cell-inflamed tumors compared with T-cell-inflamed tumors, suggesting that FGFR3-altered tumors may be resistant to immunotherapy[64]. However, clinical data from the IMvigor-210/211, CheckMate-275, and PURE-01 studies have not reported statistically significant associations between FGFR3 status and response to PD-1/PD-L1 inhibition[65-66]. Phase 2 studies have shown activity of erdafitinib, pemigatinib, and infigratinib in FGFR3-altered urothelial carcinoma with ORRs ranging from 25-40%[47,51-52]. Early analysis of the Phase 2 FIERCE-21 study for patients with pretreated urothelial carcinoma harboring FGFR3 mutations or fusions showed better median PFS when vofatamab was combined with docetaxel relative to vofatamab alone (not reached vs. 4 months)[62]. Interim analysis of the Phase 2 FIERCE-22 trial evaluating vofatamab combined with pembrolizumab for patients with pretreated urothelial cancer reported an ORR of 36% (8/22) with responses observed for 33% (5/15) and 43% (3/7) of patients with wildtype or mutated and/or rearranged FGFR3, respectively[63]. In a Phase 1 study, rogaratinib elicited an ORR of 24% (12/51, 1 CR) and a DCR of 73% (37/51) in advanced urothelial carcinoma with FGFR1, FGFR2, or FGFR3 mRNA overexpression[53].

FREQUENCY & PROGNOSIS

FGFR3 mutation and amplification have been reported in 26-59% and 18% of bladder urothelial carcinoma cases, respectively[18,67-69]. FGFR3 mutations are detected more frequently in upper tract urothelial carcinoma (26-40%) compared to bladder urothelial carcinoma (19-26%)[70-72]. S249C has been reported to be the most frequent FGFR3 mutation in urothelial tumors, with similar incidences of 62% and 58% in bladder tumors and upper urothelial tract tumors, respectively[67]. FGFR3 and TP53 have been reported to be the most frequently mutated genes in bladder cancer, and it has been suggested that urothelial carcinomas develop through at least two molecular pathways: one related to FGFR3, typically in less invasive tumors, and one related to TP53, characterized by higher grade invasive tumors[73]. FGFR3 expression has been found in 70% of bladder urothelial carcinomas, with high expression in 36% and 22% of low-grade and high-grade samples, respectively[68]. FGFR3 mutation has been associated with low tumor stage in bladder tumors and with a lower risk of death in patients with bladder tumors by univariate analysis but not multivariate analysis[67].

FINDING SUMMARY

FGFR3 (Fibroblast growth factor receptor 3) encodes a receptor tyrosine kinase that typically promotes cell cycle progression and angiogenesis via activation of downstream signaling pathways, including RAS-MAPK and AKT; gain of function mutations in FGFRs have been reported in several cancer types[74-76]. Missense alterations such as seen here have been demonstrated to be activating and are predicted to be oncogenic[77-96]. Several FGFR3 germline alterations, including A391E, G380R, S249C, Y373C, and K650 mutations, have been associated with skeletal dysplasias of varying severity[80-82,85,91,95,97-104].

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GENE
ERBB2

ALTERATION
S310F

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
929C>T

VARIANT ALLELE FREQUENCY (% VAF)
37.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[105-110], pertuzumab in combination with trastuzumab[107,111-113], and zanidatamab (ZW25)[114], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[115] and fam-trastuzumab deruxtecan[116], HER2 kinase inhibitors such as tucatinib[117-120], and dual EGFR/HER2 kinase inhibitors such as lapatinib[121-129], afatinib[110,130-139], neratinib[140-143], dacomitinib[144], and pyrotinib[145-146]. A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17% (4/23) for ERBB2-altered solid tumors, with PRs for 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[147]. Patients with ERBB2-mutated non-small cell lung cancer (NSCLC) have also benefited from pyrotinib (30-53% ORR)[148].

FREQUENCY & PROGNOSIS

ERBB2 mutations and amplification have been found in 9-10% and 5-9% of bladder urothelial carcinoma samples[18,149], and amplifications have been reported at a higher frequency in lymph node metastases[150-151]. One study reported enrichment for ERBB2 mutations in micropapillary urothelial carcinoma (MPUC; 40% of samples), as compared with non-MPUC urothelial carcinomas (9% of samples)[152]. HER2 overexpression has been identified in 19% of bladder urothelial cancers with enrichment in Grade 3 and muscle-invasive tumors[153-154]. Studies have generally reported inconsistent results with respect to the prognostic value of HER2 expression in patients with bladder urothelial carcinoma[155].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. S310 is located in the HER2 extracellular domain and mutations at this position, including S310F and S310Y, have been reported to be activating[156-157]. In clinical studies, patients with the ERBB2 S310F mutation have benefited from ERBB2-targeted therapies including trastuzumab, pertuzumab, and lapatinib[107,125]; a patient with concurrent EGFR L858R and ERBB2 S310F mutations also reported a complete and durable response to the dual EGFR/ERBB2 inhibitor afatinib[158].

GENE
ARID1A

ALTERATION
Q1537*, S1930*

TRANSCRIPT ID
NM_006015, NM_006015

CODING SEQUENCE EFFECT
4609C>T, 5789C>A

VARIANT ALLELE FREQUENCY (% VAF)
42.8%, 42.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[159]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[160]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[161]. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[162]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[163-164], which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[165-167]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[168]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[169-170] and to 5-fluorouracil in colorectal cancer cell lines[171]. Limited clinical evidence indicates that ARID1A-altered urothelial cancer may be sensitive to pan-HDAC inhibitors; a retrospective analysis reported a CR to belinostat and a PR to panobinostat in patients with ARID1A alterations[172].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, Jan 2022)[173-181]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[168,182-185], CRC[168,186-188], and gastric cancer[168,189-193]. In the context of urothelial carcinomas, one study reported no association between ARID1A mutation and tumor grade[194], whereas others have reported contradictory associations between ARID1A protein loss and prognosis[195-196].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[177,192,197-203]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[177,190,198-199,204], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[205]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[206]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[205,207-208], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[209]; dual PRMT1 and PRMT5 inhibition may be more effective[210-212]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[213-223]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[224].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[225-226]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[227], gastrointestinal stromal tumors[228], mantle cell lymphoma (MCL)[229], melanoma[230-231], gastric cancer[232], myxofibrosarcoma[233], nasopharyngeal carcinoma[234], ovarian carcinoma[225] and non-small cell lung cancer[235]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[236] or in astrocytoma[237]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[238], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[239]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[240-241], esophageal cancer[242-243], osteosarcoma[244], and CRC[245].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[246-247]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[227,248-249], thereby reducing intracellular arginine methylation[205,207,250] and altering cell signaling[249,251]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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GENE
TSC1

ALTERATION
Q527*

TRANSCRIPT ID
NM_000368

CODING SEQUENCE EFFECT
1579C>T

VARIANT ALLELE FREQUENCY (% VAF)
54.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC1 can activate mTOR signaling[252-253]; however, response rates for patients with TSC1-mutated solid tumors treated with MTOR inhibitors such as everolimus and temsirolimus have been low[254-256]. In the prospective NCI-MATCH study, the ORR for patients with various TSC1-mutated solid tumors treated with everolimus was 7.7% (1/13); the single response was reported for a patient with urothelial cancer[254]. In TSC1-mutated renal cell carcinoma (RCC), although responses to MTOR inhibitors have been described in multiple case series and reports[257-261], retrospective analysis of a broader cohort showed no responses in TSC1-mutated RCC (0/7)[255]. 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[256]. PRs have been reported for patients with TSC1-altered perivascular epithelioid cell tumors[262-263] and epithelial ovarian carcinoma[264] treated with nab-sirolimus.

FREQUENCY & PROGNOSIS

TSC1 mutations have been reported in up to 9% of bladder urothelial carcinomas[18,149,265-268]. Loss of heterozygosity of TSC1 has been observed in up to 54% of bladder urothelial carcinomas[269-271]. Low expression of Hamartin has been associated with an increased risk of progression in bladder urothelial carcinoma[272].

FINDING SUMMARY

TSC1 encodes the protein Hamartin, which interacts with Tuberin, the gene product of TSC2, to inhibit and regulate mTOR activity[252,273]. Alterations such as seen here may disrupt TSC1 function or expression[274-276].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TSC1 variants observed here has been described in the ClinVar database as a pathogenic or likely pathogenic germline mutation (by an expert panel or multiple submitters) associated with tuberous sclerosis complex (ClinVar, Sep 2021)[277]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in TSC1 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma[278-279]. TSC1 mutations account for approximately 10 to 30% of reported sporadic cases[280]. 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[281]. In the appropriate clinical context, germline testing of TSC1 is recommended.

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[282-285]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[286-287], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[288-294]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[295-296], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[289,291-292,297-299].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, concurrent homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of cases, and CDKN2A mutation has been found in 5.5% of cases[18]. Loss of CDKN2A/B or loss of p14ARF, p16INK4a, or p15INK4b protein expression occurs frequently in bladder urothelial carcinoma, with reports of frequency ranging from 18% to 77%[266,300-307]. Several studies have associated loss of CDKN2A/B or loss of p16INK4a and p15INK4b expression with disease progression, decreased recurrence-free disease, and poor prognosis in patients with urothelial carcinoma, although results have been inconsistent[300-301,303,305,308-311].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[312-313]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[314-315]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[316-317]. One or more alterations observed here are predicted to result in p16INK4a loss of function[318-339]. One or more alterations seen here are predicted to result in p14ARF loss of function[322,339-342]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[343].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[344]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[345-346]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[347-349]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[350-352]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
KDM6A

ALTERATION
Q147*

TRANSCRIPT ID
NM_021140

CODING SEQUENCE EFFECT
439C>T

VARIANT ALLELE FREQUENCY (% VAF)
40.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to address KDM6A alterations in cancer.

FREQUENCY & PROGNOSIS

KDM6A mutations have been reported in 3.9% of samples analyzed, with the highest incidence in tumors of the urinary tract (31%), liver (7.3%), endometrium (6.7%), salivary gland (6.0%), and pancreas (5.1%) (COSMIC, Jan 2022)[173]. KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)[353], adenoid cystic carcinoma (6.7%)[354], and metastatic prostate cancer (10%)[355]. KDM6A inactivation has been found as a recurrent tumorigenic event in male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to therapies targeting histone H3 lysine 27 methylation in preclinical assays[356]. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer[357-359].

FINDING SUMMARY

KDM6A encodes a histone H3 lysine 27 demethylase UTX, which functions as a transcriptional regulator[360]. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor[360].

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GENE
LYN

ALTERATION
E241D

TRANSCRIPT ID
NM_002350

CODING SEQUENCE EFFECT
723G>T

VARIANT ALLELE FREQUENCY (% VAF)
27.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinases including LYN (specifically at low nanomolar concentration)[361-362], and other kinases, and has been approved to treat chronic myelocytic leukemia (CML) and acute lymphoblastic leukemia (ALL). A pediatric patient with relapsed B-cell acute lymphoblastic leukemia and an NCOR1-LYN fusion achieved complete remission after 2 weeks of treatment with dasatinib[363]. Similarly, a preclinical study showed that treatment with dasatinib significantly increased survival in a xenograft model of leukemic blast cells harboring NCOR1-LYN[364]. In preclinical studies of LYN-expressing breast and prostate cancer, dasatinib has been reported to inhibit cell migration and invasion[361,365]. However, amplification or other genomic alterations in LYN in solid tumors, and their potential predictive value for sensitivity of these tumors to dasatinib and other kinase inhibitors, remains poorly understood.

FREQUENCY & PROGNOSIS

LYN alterations are rare in solid tumors[366-367]. However, LYN amplification has been reported more frequently, including in ovarian (3.1%), melanoma (2.3%), prostate (2.2%), breast (1.9%), and endometrial (1.6%) cancers[366-367]. LYN expression and activation have also been reported in several types of solid tumors, including glioblastoma[368], prostate cancer[369], head and neck squamous cell carcinoma (HNSCC)[370], Ewing sarcoma[371], and breast cancer[365]. High LYN expression was associated with lower survival rates for patients with breast, colorectal, and renal cancers[365,372-373].

FINDING SUMMARY

LYN encodes a SRC family intracellular membrane-associated tyrosine protein kinase. LYN is expressed predominantly in hematopoietic cells and conveys signals from the B-cell receptor (BCR) and other receptors to activate the PI3K, STAT, and other signaling pathways[374-375].

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
51.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[376]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[377]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[378].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been observed in a variety of solid tumors, including bladder cancer[379-387]. One study reported TERT promoter mutations in 67% (14/21) of high-grade and 56% (34/61) of low-grade bladder carcinomas[379], while another study demonstrated that 85% (44/52) of all bladder cancer samples and 88% (7/8) of bladder cancer cell lines exhibited TERT promoter alteration[386]. TERT promoter mutations correlated with increased TERT mRNA expression in urothelial cancer cells[388]. In patients with bladder urothelial carcinoma, both TERT promoter mutations and increased TERT expression associate with poor prognosis, although carrying an additional germline alteration at -245 (rs2853669) may confer a better prognosis[382,388-389].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[390]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[391-393]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[379-380,394], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[394].

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Atezolizumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

In the IMvigor130 study, patients with metastatic urothelial carcinoma harboring TMB-high (>10 muts/Mb) and PD-L1 expression >5% experienced improved OS with atezolizumab monotherapy compared to platinum-based chemotherapy (HR=0.22)[397]. As second-line therapy for advanced urothelial carcinoma in the Phase 3 IMvigor211 study, atezolizumab compared with chemotherapy did not significantly improve median OS (11.1 vs. 10.6 months, HR=0.87) for patients with PD-L1 expression on 5% or more of tumor-infiltrating immune cells[13]. The ORRs (23% vs. 22%) and median PFSs (HR=1.01) were similar between the treatment arms, but atezolizumab was associated with a numerically longer median duration of response (15.9 vs. 8.3 months)[13] The Phase 3 IMvigor130 study for patients with treatment-naive urothelial carcinoma found that the addition of atezolizumab to platinum-based chemotherapy improved median PFS (8.2 vs. 6.3 months, HR=0.82) and numerically improved median OS (16.0 vs. 13.4 months, HR=0.83) compared to placebo, with similar ORRs (47.4% vs. 43.8%) but a higher CR rate (12.5% vs. 6.8%)[398]. In a Phase 2 study, patients with metastatic urothelial carcinoma treated with atezolizumab as first-line therapy experienced an ORR of 23%, a CR rate of 9%, and a clinical benefit rate of 30%[12]. Another Phase 2 trial of atezolizumab as second-line therapy reported an ORR of 15%, with 80% (37/46) of the responses ongoing at the median follow-up of 14.4 months; the median PFS was 2.11 months, and the 12-month OS rate was 37%[11,399]. Long-term follow-up of a Phase 1 expansion cohort reported a 3-year OS rate of 27% on second-line atezolizumab[400]. Multiple studies have reported superior ORR and OS outcomes with atezolizumab monotherapy for patients with higher tumor mutational burden (TMB) or PD-L1 expression compared to those with lower TMB or PD-L1 expression[11-13,397].

Avelumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

The Phase 3 JAVELIN Bladder 100 trial of maintenance avelumab for patients with advanced or metastatic urothelial cancer reported longer median PFS (mPFS; 3.7 vs. 2.0 months, HR=0.62), higher ORR (9.7% vs. 1.4%), and longer median OS (mOS; 21.4 vs. 14.3 months, HR=0.69) for avelumab plus best supportive care (BSC) as compared with BSC in the randomized population; longer mPFS (5.7 vs. 2.1 months, HR=0.56), higher ORR (13.8% vs. 1.2%), and longer mOS (not reached vs. 17.1 months, HR=0.56) were also reported for the PD-L1-positive population[401]. In the Phase 2 JAVELIN Medley VEGF study, avelumab plus axitinib yielded an ORR of 10% (2/20) and mPFS of 2.3 months for patients with treatment-naive, cisplatin-ineligible urothelial carcinoma[402].

Dostarlimab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

Clinical data on the efficacy of dostarlimab for the treatment of urothelial carcinoma are limited (PubMed, Nov 2021). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[403-405]. 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[403,406].

Erdafitinib

Assay findings association

FGFR3
S249C

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence, FGFR3 fusions[48,407-409] and activating mutations[47-48,408] may confer sensitivity to erdafitinib.

SUPPORTING DATA

A Phase 2 study evaluating erdafitinib to treat patients with unresectable or metastatic urothelial carcinoma (UC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an overall ORR of 40% (4 CRs) and a DCR of 80%[410]. Patients with only FGFR2/3 fusions achieved a median PFS (mPFS) of 2.8 months and a median OS (mOS) of 10 months, and patients with only FGFR3 mutations had an mPFS of 5.6 months and an mOS of 12 months[410]. Patients with prior immunotherapy experienced an ORR of 59% (13/22)[47], mPFS of 5.7 months, and mOS of 11 months in this trial[410]. A Phase 1 study reported a similar ORR (43%, 10/23) for patients with advanced UC and FGFR alterations treated with erdafitinib[48,411]. The Phase 2 NORSE study evaluating erdafitinib alone or in combination with the PD-1 antibody cetrelimab to treat patients with metastatic or locally advanced UC harboring FGFR mutations or fusions reported ORRs of 33% (6/18, 1 CR) and 68% (13/19, 4 CRs) and DCRs of 100% (18/18) and 94% (17/18) for the single-agent and combination-agent arms, respectively[412].

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Nivolumab

Assay findings association

Tumor Mutational Burden
11 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 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, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

The Phase 2 CheckMate 275 and Phase 1/2 CheckMate 032 studies evaluating nivolumab for patients with platinum-refractory metastatic urothelial carcinoma (UC) reported ORRs of 20% (6.3% CR) and 26% (10.3% CR), PFS of 1.9 and 2.8 months, and OS of 8.6 and 9.9 months, respectively[413-415]. CheckMate 032 additionally reported a 38% ORR, 4.9 month median PFS (mPFS), and 15.3 month median OS for patients treated with nivolumab and ipilimumab; a 58% ORR was observed for patients with ≥1% tumor PD-L1 expression[413]. In a Phase 3 trial of neoadjuvant nivolumab and ipilimumab for patients with high-risk advanced UC, 60% (9/15) of patients with a combined positive PD-L1 score ≥10 experienced a pathologic CR compared with 22% (2/9) of patients with lower PD-L1 expression[416]. A Phase 2 study of ipilimumab and nivolumab for patients with platinum-refractory metastatic UC who progressed on nivolumab monotherapy observed PRs for 23% (5/22) of patients[417]. The Phase 3 CheckMate-274 study of adjuvant nivolumab versus placebo following radical surgery for patients with high-risk muscle-invasive UC reported an improved median disease-free survival (20.8 vs. 10.8 months) with 75% of patients treated with nivolumab alive and disease-free at 6 months versus 60% with placebo (HR=0.70); the percentages were 75% and 56%, respectively, for patients with PD-L1 expression ≥1% (HR=0.55); in an exploratory subgroup analysis, the DFS HR was 0.82 for patients with PD-L1-negative tumors[418]. A Phase 2 study of nivolumab plus chemotherapy for patients with muscle-invasive bladder cancer reported a complete clinical response (cCR) rate of 48% (31/64)[408]. An exploratory biomarker analysis of this study found an association between cCR and TMB ≥ 10 Muts/Mb (p=0.02) or ERCC2 mutation (p=0.02)[408]. Combining the multikinase inhibitor cabozantinib with nivolumab or with nivolumab plus ipilimumab demonstrated activity for immunotherapy-naive patients with chemotherapy-refractory metastatic UC (ORR of 50% [6/12] and 22% [2/9], respectively; mPFS of 24 and 10 months, respectively); cabozantinib combined with nivolumab also benefited immunotherapy-refractory patients (ORR of 29% [2/7])[419] and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma or bladder adenocarcinoma[420]. Addition of the IDO1 inhibitor BMS986205 to nivolumab in previously treated advanced UC elicited ORRs for 37% (3/27 CRs, 7/27 PRs) of immunotherapy-naive patients but no responses for 3 patients who had prior immunotherapy[421]. As first-line therapy for advanced UC, nivolumab combined with the immunostimulatory therapy bempegaldesleukin achieved an ORR of 48% (13/27; 5/27 CRs), with 50% (6/12) of PD-L1-positive and 45% (5/11) of PD-L1-negative patients responding[422].

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Pembrolizumab

Assay findings association

Tumor Mutational Burden
11 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 (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), 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 melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell 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, 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 clinical data across solid tumors[2-4,395-396], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

In the Phase 2 PURE-01 study of neoadjuvant pembrolizumab for muscle-invasive bladder urothelial carcinoma, TMB was significantly associated with the probability of pathologic CR (pCR) but was not an independent marker of pCR probability[423]. For TMB ≤11 Muts/Mb, the probability of pCR was not dependent on the PD-L1 combined positive score (CPS); however, increased CPS was associated with increased pCR probability for TMB >11 Muts/Mb[423]. The Phase 3 KEYNOTE-045 trial for patients with advanced urothelial carcinoma found second-line pembrolizumab superior to chemotherapy for median OS (10.1 vs. 7.3 months, HR=0.74) and ORR (21% vs. 11%), but not PFS (2.1 vs. 3.3 months, HR=0.96)[424]; a 2-year follow-up revealed PFS rates were higher for patients who received pembrolizumab (12% vs. 3.0%)[425]. First-line pembrolizumab therapy for cisplatin-ineligible patients with advanced urothelial carcinoma achieved a confirmed ORR of 29%, median DOR of 33.4 months, and median OS of 11.3 months after 5 years of follow-up in the Phase 2 KEYNOTE-052 trial. Improved median OS (18.5 months), ORR (47%, n=110, 21% CR), and median DOR (not yet reached at the 5-year mark) were observed for the subset of patients with a PD-L1 combined positive score (CPS) ≥10, compared with a median OS of 9.7 months, an ORR of 21% (n= 251, 4% CR), and a DOR of 21.2 months for the subset of patients with a PD-L1 CPS <10[426]. The Phase 2 PURE-01 study investigated neoadjuvant pembrolizumab followed by radical cystectomy in muscle-invasive urothelial bladder carcinoma (MIBC) and reported pathologic CRs for 40% (17/43) of patients; there was a significant association between CR rate and PBRM1 mutation (p=0.0024)[427]. For patients with high-risk non-MIBC unresponsive to the Bacillus Calmette-Guerin vaccine, follow-up analysis from the Phase 2 KEYNOTE-057 trial reported a 3-month CR rate of 40% (41/102) for patients treated with pembrolizumab, 75% and 53% of whom experienced a CR duration of at least 6 months and 12 months, respectively[428]. In a Phase 1b/2 trial, treatment of patients with advanced urothelial cancer with combination pembrolizumab and lenvatinib elicited an ORR of 25% (5/20, 1 CR) and median PFS of 5.4 months[429].

Ado-trastuzumab emtansine

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[115,430-445] .

SUPPORTING DATA

Clinical data on the efficacy of ado-trastuzumab emtansine for the treatment of urothelial carcinoma are limited (PubMed, Feb 2022). The vast majority of data on the therapeutic use of T-DM1 have been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. Phase 2 basket trials for HER2-amplified cancers have reported ORR of 8-28% with T-DM1, including responses in salivary gland, lung, endometrial, biliary tract, and ovarian cancers[431,438]. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy[434]. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[115,435] . Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively[436-437] .

Cemiplimab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of urothelial carcinoma are limited (PubMed, Nov 2021). Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[446]. 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[447-448] . 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[449].

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Durvalumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,395-396] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Biomarker analysis of the Phase 3 DANUBE trial for patients with locally advanced or metastatic urothelial carcinoma reported that a blood TMB (bTMB) score ≥24 Muts/Mb (approximately 12 Muts/Mb as measured by this assay) or tissue TMB (tTMB) score ≥10 Muts/Mb was associated with improved survival following combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab compared with chemotherapy; neither bTMB nor tTMB was associated with better outcomes following treatment with durvalumab alone[450]. In the first-line setting for locally advanced or metastatic urothelial carcinoma, the randomized, controlled, Phase 3 DANUBE study showed that durvalumab monotherapy did not significantly improve median OS for patients with PD-L1 high tumor status compared with chemotherapy (14.4 vs. 12.1 months, HR=0.89, p=0.30); durvalumab plus tremelimumab also did not improve median OS in the intention-to-treat population (15.1 vs. 12.1 months, HR=0.85, p=0.075)[451-452] . For chemotherapy-pretreated patients with advanced urinary tract carcinoma, the Phase 3b STRONG study of durvalumab reported an ORR of 18% and mOS of 7.0 months, with longer mOS observed for patients with high PD-L1 expression (9.3 vs. 6.5 months)[453]. The Phase 2 DUART study of concurrent durvalumab and radiation therapy followed by adjuvant durvalumab for patients with locally advanced bladder urothelial carcinoma reported a 65% (13/20) ORR and 70% (14/20) DCR; median PFS was 18.5 months and median OS was not reached, but 1- and 2- year OS probabilities were 84% and 77%, respectively[454]. In a Phase 1 study of durvalumab with tremelimumab in a cohort of patients with platinum-refractory metastatic urothelial cancer, an ORR of 21% (35/168, 4 CRs), a median PFS of 1.9 months, and an OS of 9.5 months were reported[455]. For patients with localized muscle-invasive bladder cancer, the Phase 2 IMMUNOPRESERVE-SOGUG study of durvalumab plus tremelimumab with concurrent radiotherapy reported a CR rate of 81% (26/32), 12-month DFS rate of 76%, 12-month bladder intact DFS rate of 73%, and 12-month OS rate of 87%[456]. Interim results from the Phase 2 ARCADIA study evaluating the combination of durvalumab and cabozantinib to treat patients with advanced urothelial carcinoma following progression on platinum chemotherapy reported an ORR of 38% (6/16, 2 CRs)[457]. Combining durvalumab with matched targeted therapies (FGFRi, PARP, or mTOR inhibitors) did not improve PFS or OS for patients with platinum-refractory advanced urothelial cancer in the Phase 2 BISCAY study[458]. In the neoadjuvant setting, a Phase 2 study of durvalumab and olaparib yielded an ORR of 14% (4/29) for patients with muscle-invasive bladder carcinoma[459].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[460-461] , ERBB2 mutation may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

Clinical data on the efficacy of fam-trastuzumab deruxtecan for the treatment of urothelial carcinoma are limited (PubMed, Feb 2022). Fam-trastuzumab deruxtecan has demonstrated activity in multiple ERBB2-positive cancer types. In the Phase 2 DESTINY trials, clinical benefit was observed for patients treated with fam-trastuzumab deruxtecan monotherapy who had previously treated, HER2-expressing breast (60.9% ORR, median PFS 16.4 months)[116], colorectal (45.3% ORR, median PFS 6.9 months)[462], or gastric or gastroesophageal cancer (42.8% ORR, median PFS 5.6 months)[463], as well as HER2-mutated lung cancer (61.9% ORR, median PFS 14.0 months)[464]. In a Phase 1 study evaluating single-agent fam-trastuzumab deruxtecan for the treatment of patients with ERBB2-mutated solid tumors or ERBB2-expressing solid tumors other than breast or gastric cancer, the median PFS was 7.2 months and the ORR was 28.3% (17/60), with responses reported for patients with non-small cell lung carcinoma, breast cancer, colorectal cancer, salivary gland carcinoma, cholangiocarcinoma, and endometrial cancer[460].

Infigratinib

Assay findings association

FGFR3
S249C

AREAS OF THERAPEUTIC USE

Infigratinib is a TKI that inhibits FGFR1, FGFR2, and FGFR3. It is FDA approved for the treatment of patients with unresectable locally advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on clinical activity in urothelial carcinoma[51-52,465-466] , FGFR3 rearrangements or mutations may predict sensitivity to infigratinib.

SUPPORTING DATA

Following a Phase 1 study that showed activity of infigratinib for patients with FGFR3-mutated urothelial carcinoma[465], a Phase 2 study of infigratinib for patients with urothelial carcinoma harboring either FGFR3 mutations or rearrangements and ineligible for platinum chemotherapy reported an ORR of 25% (17/67) and DCR of 64% (43/67); median PFS and OS were estimated to be 3.75 and 7.75 months, respectively[51]. In this Phase 2 study, most responses were reported for patients with FGFR3-mutated tumors; however, a CR was reported for a patient with urothelial carcinoma harboring an FGFR3 rearrangement[51]. Additional analysis of this Phase 2 study showed improved ORR (50% [4/8] vs. 22% [13/59]) and survival for patients with upper tract urothelial carcinoma relative to those with bladder urothelial carcinoma[52]. Responses to infigratinib have been reported for multiple patients with non-muscle invasive bladder cancer, including CR in 1 patient with an FGFR3-rearranged tumor and 2 patients with FGFR3-mutated tumors[466].

Lapatinib

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[121-129] .

SUPPORTING DATA

Lapatinib has shown limited clinical benefit for the treatment of urothelial carcinoma. A Phase 3 study of lapatinib or placebo in patients with EGFR or ERBB2-positive metastatic urothelial bladder cancer who progressed on first-line chemotherapy reported no significant difference in PFS or OS[467]. A Phase 2 study of single-agent lapatinib in patients with urothelial carcinoma did not meet its primary endpoint of objective response rate, but clinical benefit was observed, particularly in patients with EGFR or ERBB2 amplification[468]. A small study of six patients with metastatic transitional cell carcinoma treated with paclitaxel and lapatinib reported negative side effects; most patients discontinued therapy[469]. A trial of lapatinib, gemcitabine, and cisplatin as a neoadjuvant regimen for patients intending to undergo radical cystectomy reported substantial treatment-related toxicity and the study was terminated early[470].

Neratinib

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[140-143,471-473] and preclinical[474-478] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

The Phase 2 SUMMIT study reported no responses (0/16) for patients with ERBB2-mutated bladder cancer treated with neratinib[142]. Neratinib has been largely evaluated in the context of breast cancer and non-small cell lung cancer (NSCLC). For patients with advanced HER2-positive breast cancer, neratinib treatment resulted in PFS of 22.3 weeks for patients with prior trastuzumab treatment and 39.6 weeks for those with no prior trastuzumab treatment[479]. In patients with HER2-positive breast cancer with brain metastases, neratinib elicited a CNS ORR of 8% (3/40)[480]. In a Phase 3 study of patients with HER2-positive, early stage breast cancer previously treated with trastuzumab, neratinib significantly improved the 2-year invasive disease-free survival compared to placebo (HR=0.67, p=0.0091)[472]. In Phase 2 trials of single-agent neratinib for patients with ERBB2-mutated, non-amplified metastatic breast cancer, clinical benefit rates of 31-40% and median PFS of 3.5-4 months have been achieved[141-143] . Neratinib in combination with various other agents has also shown significant clinical activity against breast cancer[473,481-486] . In patients with ERBB2-mutated NSCLC, where the majority of cases harbor inhibitor-resistant exon 20 insertions, neratinib monotherapy has resulted in ORRs of 0-4%[142,471,487-488] . However, clinical outcomes have been improved by combination of neratinib with other targeted agents, such as temsirolimus or trastuzumab[471,487-488] . Trials of neratinib have shown high ORRs (up to 44%) in ERBB2-mutated cervical cancer[142,489] but very low ORRs in colorectal and bladder cancer[142].

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Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,490] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

A Phase 2 study of ipilimumab and nivolumab for patients with platinum-refractory metastatic UC who progressed on nivolumab monotherapy observed PRs for 23% (5/22) of patients[417]. The Phase 1/2 CheckMate 032 reported a 38% ORR, a 4.9 month median PFS, and a 15.3 month median OS for patients with locally advanced or metastatic UC treated with nivolumab and ipilimumab; a 58% ORR was observed for patients with ≥1% tumor PD-L1 expression[413]. A Phase 2 study of nivolumab in combination with ipilimumab for patients with advanced bladder cancers reported 1 CR in a patient with plasmacytoid carcinoma and 2 PRs in patients with small cell carcinoma[491]. A Phase 1 trial of nivolumab plus ipilimumab and cabozantinib in patients with refractory metastatic UC and other genitourinary cancers reported a 42% ORR among patients with metastatic UC and bladder squamous cell carcinoma[492]. In the Phase 1 NABUCCO study of neoadjuvant ipilimumab plus nivolumab for patients with advanced urothelial cancer, 93% (23/24) of patients underwent resection within 12 weeks and 46% (11/24) had a pathological CR[493].

Trastuzumab

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[105-106,110,125,494-498] .

SUPPORTING DATA

A multi-center, randomized Phase 2 study comparing trastuzumab in combination with gemcitabine and platinum chemotherapy to chemotherapy alone for the treatment of patients with urothelial carcinoma reported no significant difference in progression-free survival (PFS), objective response rate, or median overall survival between the two treatment arms; however, the authors noted that only 13% (75/563) patients in this study were HER2-positive[499]. In a Phase 2a umbrella basket trial, out of 9 patients with bladder cancer and HER2 alteration, 1 patient had a complete response, 2 patients had a partial response, and 2 patients had stable disease[500]. Trastuzumab has been reported to show activity in combination with chemotherapy in patients with HER2-positive urothelial carcinoma, but the relative benefit is difficult to ascertain without Phase 3 data[501-502] .

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Trastuzumab + Pertuzumab

Assay findings association

ERBB2
S310F

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[112,496,503-507] .

SUPPORTING DATA

In a Phase 2 trial for patients with advanced bladder cancer harboring ERBB2 amplification or overexpression, treatment with trastuzumab plus pertuzumab resulted in an ORR of 18% (4/22)[496,508] .

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

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

BIOMARKER

Tumor Mutational Burden

RESULT

11 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

NCT03682068

PHASE 3

Study of Durvalumab Given With Chemotherapy, Durvalumab in Combination With Tremelimumab Given With Chemotherapy, or Chemotherapy in Patients With Unresectable Urothelial Cancer

TARGETS
CTLA-4, PD-L1

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Xiamen (China), Hangzhou (China), Shanghai (China), Nanchang (China), Suzhou (China), Nanjing (China), Guangzhou (China)

NCT04223856

PHASE 3

Enfortumab Vedotin and Pembrolizumab, With or Without Chemotherapy, vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer

TARGETS
PD-1, Nectin-4

LOCATIONS: Taipei (Taiwan), Kweishan (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Hwasun (Korea, Republic of), Fukuoka (Japan), Ube (Japan), Daejeon (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04241185

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) Versus CRT Alone in Muscle-invasive Bladder Cancer (MIBC) (MK-3475-992/KEYNOTE-992)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagasaki (Japan), Daejeon (Korea, Republic of), Seongnam-si (Korea, Republic of), Songpagu (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Takatsuki (Japan), Tokyo (Japan)

NCT03674567

PHASE 1/2

Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination With Pembrolizumab

TARGETS
PD-1, CCR4

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Busan (Korea, Republic of), Shatin (Hong Kong), High West (Hong Kong), Ulsan (Korea, Republic of), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand)

NCT03661320

PHASE 3

A Study of Chemo Only Versus Chemo Plus Nivo With or Without BMS-986205, Followed by Post-Surgery Therapy With Nivo or Nivo and BMS-986205 in Patients With MIBC

TARGETS
IDO1, PD-1

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Fukuoka (Japan), Gyeongsangnam-do (Korea, Republic of), Daegu (Korea, Republic of), Seongnam-si (Korea, Republic of), Seongnam-si, (Korea, Republic of), Seoul (Korea, Republic of)

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing (China), Chengdu City (China)

NCT03861793

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of Subcutaneously-Administered Cytokine (ALKS 4230) as a Single Agent and in Combination With Anti-PD-1 Antibody (Pembrolizumab) in Subjects With Select Advanced or Metastatic Solid Tumors (ARTISTRY-2)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Suwon (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Edmonton (Canada), Badalona (Spain), Rotterdam (Netherlands), Valencia (Spain), Madrid (Spain)

NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/ Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Kashiwa (Japan), Afula (Israel), Jerusalem (Israel), Tel Aviv (Israel), Warszawa (Poland), Oslo (Norway)

NCT04261439

PHASE 1

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

TARGETS
PD-1

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

GENE
ARID1A

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

ALTERATION
Q1537*, S1930*

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Hangzhou (China), Nanjing (China), Wuhan (China), Xi'an (China), Osaka (Japan), Beijing (China), Hirakata-shi (Japan), Takatsuki-shi (Japan), Chengdu (China), Chuo-ku (Japan)

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), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04657068

PHASE 1/2

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

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Tennessee, Florida

NCT04802174

PHASE 1/2

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

TARGETS
ATR

LOCATIONS: Maryland

NCT02595931

PHASE 1

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

TARGETS
ATR

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

NCT04514497

PHASE 1

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

TARGETS
ATR, TOP1

LOCATIONS: Arizona, Oklahoma, Connecticut, Tennessee, Florida

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
ATR, PD-L1

LOCATIONS: Texas

NCT03978624

PHASE 2

Window of Opportunity Study of Pembrolizumab Alone and in Combinations in Bladder Cancer

TARGETS
PD-1, HDAC

LOCATIONS: North Carolina

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT01543763

PHASE 1

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

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

LOCATIONS: California

GENE
ERBB2

ALTERATION
S310F

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing (China), Chengdu City (China)

NCT04579380

PHASE 2

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

TARGETS
ERBB2, ER

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Osakasayama (Japan), Nagoya-shi (Japan), Kawasaki-shi (Japan), Chuo-ku (Japan), Tokyo (Japan), Chiba (Japan), Liege (Belgium), Edegem (Belgium)

NCT04639219

PHASE 2

A Study of T-DXd for the Treatment of Solid Tumors Harboring HER2 Activating Mutations

TARGETS
ERBB2

LOCATIONS: Seoul (Korea, Republic of), Suita-shi (Japan), Chuo-ku (Japan), Kashiwa (Japan), Copenhagen (Denmark), Napoli (Italy), Edegem (Belgium), Anderlecht (Belgium), Milano (Italy), Milan (Italy)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

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)

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT04172597

PHASE 2

A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

NCT02795156

PHASE 2

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

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

LOCATIONS: Colorado, Wisconsin, Missouri, Tennessee, Florida

NCT02122172

PHASE 2

Afatinib in Advanced Refractory Urothelial Cancer

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Illinois, New York, North Carolina, Georgia

GENE
FGFR3

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR3.

ALTERATION
S249C

NCT03390504

PHASE 3

A Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Participants With Advanced Urothelial Cancer and Selected Fibroblast Growth Factor Receptor (FGFR) Gene Aberrations

TARGETS
PD-1, FGFRs

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Niao-Sung Hsiang (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Hangzhou (China), ShangHai (China)

NCT04172675

PHASE 2

A Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Participants Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC)

TARGETS
FGFRs

LOCATIONS: Taipei (Taiwan), Taoyuan County (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Busan (Korea, Republic of), Nanjing (China), Wuhan (China), Jeollanam-do (Korea, Republic of), Daegu (Korea, Republic of)

NCT03473743

PHASE 1/2

A Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Erdafitinib Plus JNJ-63723283, an Anti-PD-1 Monoclonal Antibody, in Participants With Metastatic or Surgically Unresectable Urothelial Cancer With Selected FGFR Gene Alterations

TARGETS
PD-1, FGFRs

LOCATIONS: Taipei City (Taiwan), Taoyuan (Taiwan), Taichung City (Taiwan), Tainan (Taiwan), Kaohsiung City (Taiwan), Kaohsiung (Taiwan), Gwangju (Korea, Republic of), Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04045613

PHASE 1/2

Derazantinib and Atezolizumab in Patients With Urothelial Cancer

TARGETS
FGFRs, PD-L1

LOCATIONS: Busan (Korea, Republic of), Daejeon (Korea, Republic of), Incheon (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Birtinya (Australia), Tugun (Australia), Westmead (Australia), Canberra (Australia)

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)

NCT04492293

PHASE 2

An Efficacy and Safety Study of ICP-192 in Subjects With Bladder Urothelial Cancer

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Wuhan (China), Tianjin (China), Taiyuan (China), Beijing (China)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

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

NCT03564691

PHASE 1

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

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

LOCATIONS: Seoul (Korea, Republic of), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington, Hospitalet de Llobregat (Spain)

NCT02365597

PHASE 2

An Efficacy and Safety Study of JNJ-42756493 in Participants With Urothelial Cancer

TARGETS
FGFRs

LOCATIONS: Bangalore (India), Nadiad (India), Mira Road (East) (India), Villejuif Cedex (France), Sabadell (Spain), Barcelona (Spain), Santander (Spain), Valencia (Spain), Madrid (Spain), Santiago de Compostela (Spain)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

LOCATIONS: Chuo-Ku (Japan), Kashiwa (Japan)

GENE
MTAP

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors.

ALTERATION
loss

NCT03435250	**PHASE 1**
Study of AG-270 in Participants With Advanced Solid Tumors or Lymphoma With MTAP Loss	**TARGETS** MAT2A

LOCATIONS: Villejuif Cedex (France), Barcelona (Spain), Massachusetts, Connecticut, New York, Tennessee

GENE
TSC1

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

ALTERATION
Q527*

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)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

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)

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

Electronically signed by Erik Williams, M.D. | 17 March 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Uppsala (Sweden), Gothenburg (Sweden)

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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

NCT02321501

PHASE 1

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

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

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.

ALK
V163L

BRAF
D22N

BRCA2
H2361Y

CREBBP
S1078L

CTNNB1
L405F

DAXX
E457del

EPHB1
E623K

FANCC
Y146del

FGFR1
S134D

FGFR4
V781F

GATA6
P586L

MITF
E207G

MTOR
E2033K

PALB2
R879T

PDCD1 (PD-1)
A202_R203insGA

TGFBR2
S476F

TSC1
G1089A

WT1
S255L

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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. 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 fractional-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. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 935x

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