FOUNDATIONONE®CDx

PATIENT
Chen, Wei-Cheng

TUMOR TYPE
Head and neck adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
25 Apr 2022
ORDERED TEST #
ORD-1346479-01

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 Head and neck adenocarcinoma
NAME Chen, Wei-Cheng
DATE OF BIRTH 02 January 1966
SEX Male
MEDICAL RECORD # 36421600

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 Head and Neck
SPECIMEN ID S110-38254B (PF22053)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 29 October 2021
SPECIMEN RECEIVED 18 April 2022

Biomarker Findings

Tumor Mutational Burden - 18 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

PIK3CA E726K
APC S2223*
CCND1 amplification
CDK6 amplification - equivocal†
MTAP loss exons 6-8
CDKN2A/B CDKN2B loss, CDKN2A loss
EPHB4 amplification - equivocal†
FGF19 amplification
FGF3 amplification
FGF4 amplification
NOTCH1 P1443fs*36
TP53 R273H

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in this patient's tumor type**: Dostarlimab (p. 12), Pembrolizumab (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 17)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 18 Muts/Mb	Dostarlimab	Atezolizumab
	Pembrolizumab	Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
10 Trials *see p. 17*		Nivolumab + Ipilimumab
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)
PIK3CA - E726K	none	Everolimus
10 Trials *see p. 24*		Temsirolimus
APC - S2223*	none	none
3 Trials *see p. 19*		
CCND1 - amplification	none	none
5 Trials *see p. 20*		
CDK6 - amplification - equivocal	none	none
9 Trials *see p. 21*		
MTAP - loss exons 6-8	none	none
1 Trial *see p. 23*		

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
18 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[1-4,11]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[1]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[12] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[2]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[4,11]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. In the first-line setting for patients with advanced nasopharyngeal carcinoma (NPC), the Phase 3 JUPITER-02 study of the anti-PD-1 antibody toripalimab in combination with chemotherapy reported significantly improved median PFS relative to chemotherapy plus placebo (11.7 vs. 8.0 months, HR=0.52); median PFS improved regardless of PD-L1 status[13]. For patients with previously-treated NPC, the Phase 2 POLARIS-02 study of single-agent toripalimab reported a 20% (39/190) ORR, a 12.8-month median duration of response, a 1.9-month median PFS, and a 17.4-month median OS; activity and efficacy was not associated with either PD-L1 status or tumor mutational burden[14].

FREQUENCY & PROGNOSIS

Head and neck carcinoma, including squamous cell carcinoma and adenocarcinoma, harbors a median TMB of 3.8 mutations per megabase (muts/Mb), with a higher median TMB of 5 muts/Mb in head and neck squamous cell carcinoma (HNSCC) specifically, and 5.8% of cases [10.1% of HNSCC cases specifically] have high TMB (>20 muts/Mb)[15]. Published data investigating the prognostic implications of TMB in nasopharyngeal and sinonasal carcinoma are limited (PubMed, Oct 2021).

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[16-17] and cigarette smoke in lung cancer[18-19], treatment with temozolomide-based chemotherapy in glioma[20-21], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[22-26], and microsatellite instability (MSI)[22,25-26]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[2-4,11].

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[27-29], including approved therapies nivolumab and pembrolizumab[30]. 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)[31].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)[32-39], colorectal cancers (CRCs; 10-15%)[25,29,40-42], and gastric cancers (12-35%)[43-46] and at lower frequencies in many other tumor types, including esophageal[47], small bowel[48-52], hepatobiliary[53-59], prostate[60-62], and urinary tract carcinomas[63-65]. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy[66]. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting[32,35-36,38,67-69]. However, studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[34,37,39,68], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[42]. 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[42,70-71]. 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[41,72-73]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[41-42,71,73].

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GENE
PIK3CA

ALTERATION
E726K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
2176G>A

VARIANT ALLELE FREQUENCY (% VAF)
18.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[74-81], AKT[82-83], or mTOR[84-91]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[81]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[80]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[78-79]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[92]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[93]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[94]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[95], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[96].

FREQUENCY & PROGNOSIS

Two studies have reported PIK3CA mutation in 4.9-9.6% of nasopharyngeal carcinomas (NPC)[97-98], whereas several studies have reported that PIK3CA amplification and overexpression occur frequently in NPC, but that PIK3CA mutations are infrequent[99-104]. PIK3CA amplification and expression have been reported in 20% and 44% of NPCs, respectively[105]. PIK3CA mutations were detected in 7.1% of head and neck carcinomas (COSMIC, Jun 2021)[106]. In one study, PI3K mutations were prevalent in advanced Stage 4 HNSCC tumors and associated with tumor progression[107]. PIK3CA amplification has been found to be associated with poor prognosis in HNSCC[108-110]. PIK3CA amplification has been associated with more aggressive disease in NPC[101], although another study found that PIK3CA mutation did not affect disease-specific survival[97].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[111-112]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[107,113-133].

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GENE
APC

ALTERATION
S2223*

TRANSCRIPT ID
NM_000038

CODING SEQUENCE EFFECT
6668C>A

VARIANT ALLELE FREQUENCY (% VAF)
24.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[134], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[135-136]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[137]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[138-139].

FREQUENCY & PROGNOSIS

APC mutations have been reported in 8.2% (8/97) of sinonasal and nasal cavity tumors analyzed in COSMIC (Jan 2022)[106]. Small studies of sinonasal adenocarcinomas in the literature have reported APC mutations in 0-30% of samples[140-141]. Hypermethylation of the APC promoter, likely to result in downregulation of Apc expression, has been frequently reported various types of head and neck carcinomas, including laryngeal papilloma, nasopharyngeal carcinoma, squamous cell carcinoma (HNSCC), and mixed exocrine-neuroendocrine carcinoma of the nasal cavity[142-145]. An analysis of a mixed exocrine-neuroendocrine carcinoma of the nasal cavity found reduced Apc protein expression in the neuroendocrine component only, correlating with APC promoter methylation and copy number loss[145]. Studies on the prognostic effect of APC alterations in sinonasal and nasal cavity tumors are limited (PubMed, Mar 2021). Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[146].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[147]. Alterations such as seen here may disrupt APC function or expression[148-152].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[153-155]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[156], and in the appropriate clinical context germline testing of APC is recommended.

GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[157-162], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[161,163]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[164]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[164]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[165]. Two of 3 patients with advanced solid tumors and concurrent alterations in CCND1/3 and NOTCH1, as seen here, achieved prolonged SD on palbociclib in the exploratory analysis of NCI-MATCH[164].

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[166-167]; in these studies, CCND1 amplification was associated with significantly decreased response rate[167] and OS (HR=1.6-2.0)[166-167] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[166-167].

FREQUENCY & PROGNOSIS

Amplification of CCND1 has been observed in 28-45% of head and neck squamous cell carcinoma (HNSCC) cases, including 63% of pharyngeal carcinomas, 37% of laryngeal, and 25% of oral carcinomas[168-170]. A study reported cyclin D1 expression in 66% of HNSCC samples[171]. CCND1 amplification or overexpression has been associated with advanced disease, lymph node metastasis, and decreased overall and disease-free survival in patients with HNSCC[170-174]. CCND1 or CCND3 protein expression may also associate with cisplatin resistance in HNSCC[175].

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[176] and may lead to excessive proliferation[177-178].

GENE
CDK6

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with CDK6 activation may be sensitive to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[158-159,161,179]. Clinical benefit has been reported for patients with CDK6-amplified or mutated solid tumors in response to treatment with ribociclib[165,180] .

FREQUENCY & PROGNOSIS

No alterations in CDK6 were reported in 56 samples analyzed in the Singapore Nasopharynx TCGA dataset[99]. Published data investigating the prognostic implications of CDK6 alterations in head and neck carcinomas are limited (PubMed, Jan 2021).

FINDING SUMMARY

CDK6 encodes cyclin-dependent kinase 6, which regulates the cell cycle, differentiation, senescence, and apoptosis[181-183]. CDK6 and its functional homolog CDK4 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[184-185]. Amplification of the chromosomal region that includes CDK6 has been reported in multiple cancer types, and has been associated with overexpression of CDK6 protein[186-187].

GENE
MTAP

ALTERATION
loss exons 6-8

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[188]. 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[189]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[188,190-191], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[192]; dual PRMT1 and PRMT5 inhibition may be more effective[193-195]. 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[196-206]. 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[207].

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[208-209]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[210], gastrointestinal stromal tumors[211], mantle cell lymphoma (MCL)[212], melanoma[213-214], gastric cancer[215], myxofibrosarcoma[216], nasopharyngeal carcinoma[217], ovarian carcinoma[208] and non-small cell lung cancer[218]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[219] or in astrocytoma[220]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[221], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[222]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[223-224], esophageal cancer[225-226], osteosarcoma[227], and CRC[228].

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[229-230]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[210,231-232], thereby reducing intracellular arginine methylation[188,190,233] and altering cell signaling[232,234]. 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.

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A 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[235-238]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[239-240], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[159-160,165,180,241-243]; 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[244-245], 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[158-159,165,242,246-247].

FREQUENCY & PROGNOSIS

Mutation in CDKN2A or CDKN2B has been detected in 1.1% (1/90) and 0% (0/21) sinonasal carcinomas analyzed in COSMIC, respectively (Jan 2022)[106]. In a genomic analysis of 56 nasopharyngeal carcinoma cases, mutation of CDKN2B was detected in 2% (1/56) of samples, while CDKN2A mutation was absent[99,248-249]. In another study of nasopharyngeal carcinoma, p16INK4a homozygous deletion was observed in 35% (7/20) of cases[250]. CDKN2A and CDKN2B were identified as susceptibility loci in nasopharyngeal carcinoma[251]. Inactivation of CDKN2A and CDKN2B by gene methylation was reported to be common in undifferentiated nasopharyngeal carcinoma, with CDKN2A methylation occurring in 23-42% of cases and CDKN2B methylation occurring in 20-50% of cases[252-253]. CDKN2A is also often inactivated in head and neck squamous cell carcinoma (HNSCC) through deletion, promoter methylation, or mutation[254-256]. In the context of nasopharyngeal carcinoma, loss of p16INK4a correlated with worse overall survival[257] and local recurrence[258].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[259-260]. 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[261-262]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[263-264]. One or more alterations observed here are predicted to result in p16INK4a loss of function[265-286]. One or more alterations seen here are predicted to result in p14ARF loss of function[269,286-289]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[290].

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[291]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[292-293]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[294-296]. 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[297-299]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
EPHB4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[300], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[301]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[300,302-306]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[307-309].

FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[310-313], gastric and esophageal[314-318], colorectal carcinoma (CRC)[319-325], breast[326-330], ovarian[330-332], endometrial[333-335], thyroid[336-338], lung[339-340], glioma[341-342], and other solid tumors[302,343-350]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[302,310,326,331-332,340,343,345], histological grade[316,326,333,342], and hormone receptor status[329,334]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][324], HNSCC (HR = 2.95)[313], epithelial ovarian cancer (HR = 4.53)[330], or glioma (HR = 3.21)[342].

FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[351]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[352], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[353-354]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[355]. EPHB4 amplification has been reported in several solid tumor types[310-311,316,356-357] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[310]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[306].

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[358]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[359]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[360]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[361], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[362]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[363].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[364-366]. FGF19 mutations are rare in solid tumors[364]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[367-368], and in prostate cancer following radical prostatectomy[369]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[370] and lung SCC[371].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[372-373]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[374]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[375], lung squamous cell carcinoma[371,376], and head and neck squamous cell carcinoma (HNSCC)[370], but was not observed in other cancers[362,377].

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GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[378].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[177].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[379].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[380-381] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[380]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[378].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[177] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2022)[248-249].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[382] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[383]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[177,380,384-387] and may confer sensitivity to the multi-kinase inhibitor sorafenib[380].

GENE
NOTCH1

ALTERATION
P1443fs*36

TRANSCRIPT ID
NM_017617

CODING SEQUENCE EFFECT
4319_4320insT

VARIANT ALLELE FREQUENCY (% VAF)
56.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be potential therapeutic approaches in the case of NOTCH1 activating mutations[388-396]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PRs in 15% (6/39) and SDs in 54% (21/39) of patients with metastatic adenoid cystic carcinoma (ACC) harboring NOTCH activating alterations[397]. Additional responses to AL101 have been reported in a patient with gastroesophageal junction adenocarcinoma harboring multiple NOTCH1 mutations, a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation, and a patient with ACC harboring a single NOTCH1 mutation[398]. A Phase 1 study of the pan-NOTCH inhibitor CB-103 for patients with advanced or recurrent solid tumors reported a preliminary mPFS of 21.7 weeks for patients with ACC, with 2 patients harboring NOTCH1-mutated ACC demonstrating SD > 6 months as best response[399]. On the basis of clinical data in non-Hodgkin lymphoma, NOTCH1 activating alterations may be associated with sensitivity to the approved PI3K inhibitor copanlisib[400]; this is further supported by limited preclinical data that suggest that NOTCH1 may be a negative regulator of PTEN[401-402]. Two of 3 patients with advanced solid tumors and concurrent alterations in CCND1/3 and NOTCH1, as seen here, achieved prolonged SD on palbociclib in the exploratory analysis of NCI-MATCH[164]. While activating mutations may be targeted via gamma-secretase inhibitors or PI3K inhibitors, there are no therapies available to address NOTCH1 inactivation, as seen here.

FREQUENCY & PROGNOSIS

NOTCH1 mutation has been reported in 13% (4/30) of upper aerodigestive tract adenocarcinoma cases (COSMIC, Mar 2021)[106]. Studies have reported NOTCH1 mutations in 15-26% of head and neck squamous cell carcinomas (HNSCCs) analyzed, suggesting that NOTCH1 acts as a tumor suppressor in HNSCC[403-404]. NOTCH1 mutations have been reported in 3% of nasopharyngeal carcinoma and 22% (2/9) of sinonasal adenocarcinomas analyzed in COSMIC (Aug 2021)[106]. Published data investigating the prognostic implications of NOTCH1 alterations in head and neck adenocarcinoma are limited (PubMed, Mar 2021). Published data investigating the prognostic implications of NOTCH1 alteration in head and neck carcinomas outside of the context of HNSCC are limited (PubMed, Aug 2021).

FINDING SUMMARY

NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene[405-406]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis[407-408]. NOTCH1 alterations that disrupt ligand binding[409-411] or remove the transmembrane domain (amino acids 1736-1756), RAM domain (amino acids 1757-1926), ankyrin repeats (amino acids 1927-2122) and/or transactivation domain (amino acids 2123-2374) that are necessary for NOTCH1 function, such as observed here, are predicted to be inactivating[408,412-414]. Several point mutations, including D469G, A465T, C478F, R1594Q, and P1770S, have also been reported to inactivate NOTCH1[405,415-416].

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GENE
TP53

ALTERATION
R273H

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
818G>A

VARIANT ALLELE FREQUENCY (% VAF)
47.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[417-420], or p53 gene therapy and immunotherapeutics such as SGT-53[421-425] and ALT-801[426]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[427]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[428]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[429]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[430]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[431]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[432]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[433]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[425]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[434-436]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[437]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[438-439]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[440-441]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Mutations of TP53 have been reported in 36-51% of head and neck carcinomas, across numerous subtypes including in 40% of adenocarcinomas[442-445]. In one study of 78 patients with undifferentiated nasopharyngeal carcinoma, p53 protein expression was associated with worse disease-free survival[446].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[447]. Alterations such as seen here may disrupt TP53 function or expression[448-452].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2021)[453]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[454-456], including sarcomas[457-458]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[459] to 1:20,000[458]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[460]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[461-466]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[461-462]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[467]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[465,468-469]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Dostarlimab

Assay findings association

Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,470] , 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 head and neck cancer are limited (PubMed, Mar 2022). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[471-473] . 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[471,474] .

Pembrolizumab

Assay findings association

Tumor Mutational Burden
18 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, endometrial carcinoma that is MSI-H or dMMR, 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[2-4,12,470] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

A Phase 1b trial for 27 patients with previously treated PD-L1-positive advanced nasopharyngeal carcinoma achieved an ORR of 25.9% (7/27), a median PFS of 6.5 months, and a median OS of 16.5 months on pembrolizumab[475]. In the Phase 2 KEYNOTE 158 multi-solid tumor trial, treatment with the PD-1 inhibitor pembrolizumab led to improved ORR for patients with TMB of 10 Muts/Mb or higher compared those with TMB <10 Muts/Mb (28.3% [34/120] vs. 6.5% [41/635])[11]. In the KEYNOTE 028/012 pan-solid tumor trials, a similar improvement in ORR was reported for patients with >103 non-synonymous mutations/exome (~ equivalency >8 Muts/Mb as measured by this assay) compared to those with <103 non-synonymous mutations/exome (30.6% [11/36] vs. 6.5% [5/77])[4].

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Atezolizumab

Assay findings association

Tumor Mutational Burden
18 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[2-4,12,470] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

A Phase 1 trial of atezolizumab for patients with previously treated advanced head and neck cancer reported an ORR of 22% (7/32), a median duration of response of 7.4 months, median PFS of 2.6 months, and median OS of 6.0 months. Responses were achieved for patients with primary tumors of the oral cavity (1/7), oropharynx (3/18), larynx (2/2), and nasopharynx (1/4), and did not correlate with PD-L1 expression or HPV status[476]. A 16% (3/19) ORR was reported for a dose-expansion cohort in a Phase 1b trial of atezolizumab combined with selicrelumab to treat head and neck cancer[477]. A Phase 1 study of atezolizumab combined with the IDO1 inhibitor navoximod reported 1 PR (in head and neck squamous cell carcinoma) and 1 prolonged SD outcome among 6 patients with advanced head and neck cancer[478]. A case study reported a patient with both metastatic lung adenocarcinoma and locally advanced epipharyngeal carcinoma who experienced a PR to atezolizumab in combination with several chemotherapy agents[479]. In the prospective Phase 2a MyPathway basket study evaluating atezolizumab for patients with TMB-High solid tumors, patients with TMB ≥16 Muts/Mb achieved improved ORR (38% [16/42] vs. 2.1% [1/48]), DCR (62% [26/42] vs. 23% [11/48]), mPFS (5.7 vs. 1.8 months, HR 0.34), and mOS (19.8 vs. 11.4, HR 0.53) as compared to those with TMB ≥10 and <16 Muts/Mb[480]. In a retrospective analysis of patients with 17 solid tumor types (comprised of 47% NSCLC, 40% urothelial carcinoma, and 13% encompassing 15 other solid tumors), TMB of 16 Muts/Mb or greater was reported to be associated with an improved ORR to atezolizumab compared to chemotherapy (30% vs. 14%)[12].

Avelumab

Assay findings association

Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,470] , 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 avelumab for the treatment of head and neck adenocarcinoma are limited (PubMed, Apr 2022). The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[481], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[482], urothelial carcinoma[483], mesothelioma[484], ovarian carcinoma[485], and breast cancer[486], and from avelumab combined with axitinib in renal cell carcinoma[487]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[481,485-486] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[488-490] . Phase 3 studies are evaluating avelumab with chemoradiotherapy alone (NCT02952586) or in combination with cetuximab (NCT02999087) in patients with locally advanced head and neck squamous cell carcinoma (Jun 2021).

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Cemiplimab

Assay findings association

Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,470], 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

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[491]. 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[492-493]. 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[494]. Clinical data on the efficacy of cemiplimab for the treatment of head and neck adenocarcinoma are limited (PubMed, Apr 2022).

Durvalumab

Assay findings association

Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,470], 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 durvalumab for the treatment of head and neck adenocarcinoma are limited (PubMed, Apr 2022). Single-agent durvalumab has demonstrated efficacy in non-small cell lung cancer[495-496], and head and neck squamous cell carcinoma[497-498]. In patients with advanced solid tumors, durvalumab monotherapy has elicited disease control rates (DCRs) of 36.8–46.2% (7/19 to 12/26) in Phase 1/2 studies[499-500]. Durvalumab is also under investigation in combination with other agents in Phase 1/2 trials. In advanced melanoma, durvalumab in combination with trametinib and dabrafenib elicited ORRs and DCRs of 76.2% (16/21) and 100% (21/21) in patients with BRAF-mutant tumors, and durvalumab with trametinib elicited ORRs and DCRs of 21.4% (3/14) and 64.3% (9/14) in patients whose tumors were BRAF wild-type[501]. Durvalumab in combination with the PARP inhibitor olaparib has shown activity in patients with metastatic castration-resistant prostate cancer and progression on enzalutamide and/or abiraterone[502] and in patients with BRCA-wild-type breast or gynecological cancer[503]. Durvalumab in combination with the anti-CTLA4 antibody tremelimumab, but not durvalumab as a single-agent, has shown activity in patients with previously treated advanced germ cell tumors[504]. Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680[505], the CXCR2 antagonist AZD5069[506], or the ATR inhibitor AZD6738[507]. In patients with treatment-refractory solid tumors, concurrent durvalumab and radiotherapy achieved an ORR of 60% (6/10) for in-field evaluable lesions, including 2 CRs and 4 PRs[508].

Everolimus

Assay findings association

PIK3CA
E726K

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence[84-91] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[88-91,509-513] .

SUPPORTING DATA

Clinical data on the efficacy of everolimus for the treatment of non-squamous head and neck carcinoma are limited (PubMed, Feb 2022). A patient with lacrimal gland ductal adenocarcinoma achieved an 8 month PR after treatment with everolimus[85]. A Phase 2 study of everolimus therapy has reported no objective responses in any of nine patients with refractory head and neck squamous cell carcinoma (HNSCC)[514]. A Phase 1 trial in patients with advanced solid tumors reported that everolimus in combination with low dose weekly cisplatin showed activity in several tumor types, with three partial responses and prolonged stable disease observed in five patients out of 28 evaluable patients; one patient with oropharyngeal squamous cell carcinoma obtained stable disease after more than 6 cycles of treatments[515]. Another Phase 1 trial of everolimus in combination with docetaxel and cisplatin reported progression-free survival rate of 87.5% at one year and 76.6% at two years in patients with advanced HNSCC[516]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[517], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[518].

Nivolumab

Assay findings association

Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,470] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

A Phase 2 study of single-agent nivolumab treatment in recurrent and metastatic nasopharyngeal carcinoma showed that patients had an ORR of 20.5% and a DCR of 54.5%, with 1 CR, 8 PRs, and 15 SD out of 44 patients; the median PFS was 2.8 months and the median OS was 17.1 months, with similar PFS and OS for patients with PD-L1–negative and PD-L1–positive tumors[519]. A Phase 1/2 study of nivolumab for the treatment of patients with virus-associated tumors reported an ORR of 21% (5/24) and median PFS of 2.4 months in patients with recurrent/metastatic nasopharyngeal carcinoma; 88% (21/24) of cases were EBV-positive[520].

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Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
18 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[5-6,521] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

A Phase 2 trial of nivolumab plus ipilimumab for patients with EBV-associated advanced nasopharyngeal carcinoma in Asia reported an ORR of 30% (12/40 PRs), median PFS of 5.3 months, and median OS of 17.6 months[522].

Temsirolimus

Assay findings association

PIK3CA
E726K

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence[84-91] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[88-91,509-513] .

SUPPORTING DATA

Clinical data on the efficacy of temsirolimus for the treatment of non-squamous head and neck carcinoma are limited (PubMed, Nov 2021). A Phase 2 study evaluated temsirolimus for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after failure of platinum and cetuximab and reported a median PFS of 1.9 months and overall survival of 5.1 months[523]. Temsirolimus has been tested preclinically and in clinical trials for HNSCC, in combination with the VEGF antibody bevacizumab, and has shown significant efficacy[524]. A study assessing temsirolimus in combination with metformin in patients with advanced solid tumors reported a partial response for one patient with HNSCC, despite disease progression after treatment with docetaxel and cisplatin and subsequent treatment with zalutumumab[525]. A Phase 1 study of temsirolimus in combination with carboplatin and paclitaxel in 18 patients with HNSCC reported a partial response rate of 22% and recommended Phase 2 testing[526]. However, a Phase 2 study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory HNSCC has reported that this combination therapy was poorly tolerated, with the trial ending early after 50% (6/12) of patients withdrew from the study[527].

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

18 Muts/Mb

RATIONALE

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

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT04589845

PHASE 2

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

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

LOCATIONS: 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), Changchun (China)

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)

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)

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

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)

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Guangdong (China), Changsha (China), Wuhan (China), Jinju-si (Korea, Republic of)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

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

NCT03891953

PHASE 1

Study of Safety and Efficacy of DKY709 Alone or in Combination With PDR001 in Patients With Advanced Solid Tumors.

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Chuo ku (Japan), Dresden (Germany), Essen (Germany), Barcelona (Spain), Massachusetts, Tennessee

NCT03396445

PHASE 1

Safety and Pharmacokinetics Study of MK-5890 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Adults With Advanced Solid Tumors (MK-5890-001)

TARGETS
PD-1, CD27

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Jerusalem (Israel), Ramat Gan (Israel), Be'er Sheva (Israel), Amsterdam (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Pozuelo de Alarcon (Spain)

GENE
APC

ALTERATION
S2223*

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

NCT03833700

PHASE 1

A Study of E7386 in Participants With Advanced Solid Tumor Including Colorectal Cancer (CRC)

TARGETS
CBP, Beta-catenin

LOCATIONS: Fukuoka (Japan), Nagaizumi-cho (Japan), Chuo Ku (Japan), Kashiwa (Japan)

NCT04008797

PHASE 1

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

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

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

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

GENE
CCND1

ALTERATION
amplification

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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GENE
CDK6

RATIONALE
Tumors with CDK6 amplification may be sensitive to CDK4/6 inhibitors.

ALTERATION
amplification - equivocal

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

GENE
MTAP

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors.

ALTERATION
loss exons 6-8

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

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GENE
PIK3CA

ALTERATION
E726K

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

NCT04589845

PHASE 2

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

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

LOCATIONS: 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), Changchun (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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)

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

NCT04770246

PHASE 2

TAS-117 in Patients With Advanced Solid Tumors Harboring Germline PTEN Mutations

TARGETS
AKT2, AKT1, AKT3

LOCATIONS: Vienna (Austria), London (United Kingdom), Villejuif (France), California, Ohio, Pennsylvania, Texas

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)

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.

AKT1 R15Q	***ATM*** E2347Q	***ATR*** S1616L	***ATRX*** L1517F
BRCA1 E75K	***DAXX*** R91Q	***INPP4B*** S219R	***IRS2*** W1220*
KDM5A G284D	***KMT2A (MLL)*** E1992Q	***MED12*** S1123C	***MLL2*** S504C
MSH6 K1358fs*2	***NOTCH1*** R2549C	***P2RY8*** E323G	***PRKCI*** I156M
SGK1 E46A	***TEK*** E434K	***TYRO3*** S648F	

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*	*ETV1*
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)

Electronically signed by Erik Williams, M.D. | 25 April 2022
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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 6.1.0

The median exon coverage for this sample is 721x

Electronically signed by Erik Williams, M.D. | 25 April 2022
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