FOUNDATIONONE®CDx

PATIENT
Chou, Shu Hui

TUMOR TYPE
Cervix squamous cell carcinoma (SCC)

COUNTRY CODE
TW

REPORT DATE
11 Jan 2023

ORDERED TEST #
ORD-1536403-01

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 Cervix squamous cell carcinoma (SCC)
NAME Chou, Shu Hui
DATE OF BIRTH 02 September 1980
SEX Female
MEDICAL RECORD # 49045047

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 Cervix
SPECIMEN ID S111-68915A (PF22151)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 31 October 2022
SPECIMEN RECEIVED 03 January 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

CD274 (PD-L1) amplification
PDCD1LG2 (PD-L2) amplification
MCL1 amplification
MYCL1 amplification
NOTCH2 rearrangement exon 25
PRKCI amplification

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Pembrolizumab** (p. 9), **Nivolumab** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***CD274 (PD-L1)* -** amplification	Pembrolizumab 1	Nivolumab 2A
	Dostarlimab	Atezolizumab
		Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab + Ipilimumab
10 Trials see p. 14		
***PDCD1LG2 (PD-L2)* -** amplification	Pembrolizumab 1	Nivolumab 2A
	Dostarlimab	Atezolizumab
		Avelumab
		Cemiplimab
		Durvalumab
10 Trials see p. 16		

NCCN category

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

BIOMARKER

Microsatellite status

RESULT
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[1-3], including approved therapies nivolumab and pembrolizumab[4]. 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)[5].

FREQUENCY & PROGNOSIS

MSI has been reported at a lower frequency in cervical cancer than in endometrial cancer[6]. A non-zero level of MSI has been reported in 5-25% (n = 38-100) of cervical carcinoma cases[6-11], and was not associated with HPV infection status[7,11]. In cervical squamous cell carcinoma (SCC) specifically, MSI-L and MSI-H have been reported in 12-17% and MSI-H in 12-14% of samples, respectively (n = 50-93)[12-13], including in 18% (9/50) and 2% (1/50) of early stage cases[14]. In cervical adenocarcinoma, MSI-L has been detected in 16% (6/37) and MSI-H in 11% (4/37) of cases[15]. MSI positivity has been reported to be significantly more frequent in invasive cervical carcinoma over cervical carcinoma in situ[11] and in cervical SCC over cervical intraepithelial neoplasia[13]. Although a few studies have reported MSI positivity in cervical SCC to correlate with advanced stage[12] or poorer overall survival[13], several others have reported no association between MSI status and clinicopathologic features and/or prognosis in cervical carcinoma, including SCC[6,9-11,13-14].

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[16]. 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[16-18]. 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[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
4 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[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[22-25,32-36]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[32]; similar findings were observed in the KEYNOTE 028 and 012 trials[25]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[36]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[37]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[35]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[38] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[23].

FREQUENCY & PROGNOSIS

Squamous cell carcinoma (SCC) of unknown primary harbors a median tumor mutational burden (TMB) of 7.6 Muts/Mb, and 22% of cases have high TMB (>20 Muts/Mb)[39]. High TMB has been reported frequently in skin SCC (67% of cases)[39-40]; in 10% of lung SCC[40]; 8-13% of head and neck SCC cases and non-small cell lung carcinoma, including lung SCC cases[39]; and in additional SCC cases, including urothelial (12%), cervical (6.5%), anal (3.8%), and esophageal (2.1%)[40]. One study reported that cervical carcinoma harbors a median tumor mutational burden (mTMB) of 4.4 Muts/Mb and a TMB ≥10 Muts/Mb in 15-21% of cases[41]. For cervical squamous cell carcinoma and cervical adenocarcinoma, studies reported an mTMB of 3.7-5.4 and 1.6-3.6 Muts/Mb, respectively, and a high TMB (>20 Muts/Mb) in 6.7% and 3.6% of cases, respectively[39,42]. For patients with squamous cell carcinoma (SCC) treated with PD-L1/PD-1 inhibitors, a Kaplan-Meier analysis showed a significant association for patients with high tumor mutational burden (TMB) with longer time to treatment failure (9.9 vs. 4.4 months)[40]. In the majority of cutaneous SCC cases, high mutational burden has been attributed to UV exposure rather than defective DNA mismatch repair or polymerase activity[43-44], although one study reported a small number of cutaneous SCC cases (4/39) harboring a mutation signature similar to that of human papillomavirus-positive head and neck SCC[44]. In patients with non-small cell lung cancer (NSCLC), TMB is similar between cases with squamous and non-squamous histology[45], and increased TMB is associated with higher tumor grade and poor prognosis[46], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each) but not BRAF (10%) or KRAS (9.4%)[45]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[46-47], several other large studies did find a strong prognostic association[48-51]. For patients with advanced cervical carcinoma not treated with immunotherapy, OS did not significantly differ between patients with TMB-high (≥10 mut/Mb) and TMB-low (<10 Muts/Mb), although relatively few patients had TMB-high cervical carcinoma in this analysis (n=17)[41].

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[52-53] and cigarette smoke in lung cancer[54-55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[23-24,32].

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GENE
CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of strong clinical evidence, CD274 amplification and PD-L1 overexpression may predict sensitivity to antibodies targeting PD-L1 or PD-1. Patients with high tumor PD-L1 expression across multiple solid tumor types have exhibited improved clinical benefit with the PD-L1 antibodies atezolizumab[63-64], toripalimab[65-71], and durvalumab[72]. The PD-1 antibodies pembrolizumab, nivolumab (alone or in combination with ipilimumab), and tislelizumab have elicited significant clinical responses for patients with solid tumors[73-76] and for patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[77]. However, studies evaluating nivolumab for patients with urothelial carcinoma or tislelizumab plus sitravatinib for patients with non-small cell lung cancer (NSCLC) have shown no correlation between clinical benefit and PD-L1 expression levels[78-79] . A Phase 1 trial evaluating bintrafusp alfa, a fusion protein targeting TGF-beta and PD-L1, reported ORRs of 37% (10/27) and 86% (6/7) for patients with NSCLC characterized as PD-L1-positive or having high PD-L1 expression, respectively[80]. Preclinical studies have demonstrated that JAK2 amplification regulates PD-L1 expression[81-82]; therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for patients with PD-L1 amplification. A Phase 2 trial of the anti-PD-1 antibody sintilimab plus anlotinib as a second-line or later therapy for patients with advanced PD-L1-positive cervical cancer observed an ORR of 59% (23/39) and median PFS of 9.4 months[83].

FREQUENCY & PROGNOSIS

CD274 amplification has been identified in 2.1-23% of cervical cancer cases[84-86]. CD274 amplification was reported to correlate with increased PD-L1 protein expression in cervical SCC[86]. PD-L1 expression has been variously detected in 19-96% of cervical cancers[87-91]. In one study, PD-L1 expression was detected in 37.8% (28/74) of cervical SCC, 28.6% (2/7) of adenosquamous carcinomas and 16.7% (2/12) endocervical adenocarcinomas; none of the 6 benign cervical tissue samples were PD-L1-positive[88]. Elevated PD-L1 expression has also been reported in cervical intraepithelial neoplasia (CIN)[91-92]. The prognostic impact of CD274 amplification has not been extensively studied in the context of cervical cancer (PubMed, Jan 2023). Influence of PD-L1 expression on prognosis of patients with cervical cancer is unclear, with one study reporting increased PD-L1 expression in high-grade vs. low-grade cervical SCC cases[93], another study reporting no impact of PD-L1 expression on PFS or OS, but a trend for an inferior PFS in patients with PD-L1-positive, CD8 T cell-negative tumors (HR=0.43, P=0.053)[89] and a third study observing no impact of PD-L1 expression on patient survival[87]. Another study reported poorer survival in patients with cervical SCC with diffuse, compared with marginal, PD-L1 expression and poorer survival in patients with cervical adenocarcinoma with, versus without, PD-L1-positive macrophages[90].

FINDING SUMMARY

CD274 encodes the programmed cell death ligand 1 (PD-L1), also known as B7-H1, which is a cell surface molecule important for regulating the activity of T-cells through binding to various T-cell receptors. Although PD-L1 is a costimulatory molecule for naive T-cells, it can provide inhibitory signals to activated T-cells through interactions with the receptors PD-1 or CD80[94-95]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells[96-98]. CD274 amplification is associated with positive PD-L1 protein expression in solid tumors[84,99-100] and lymphomas[77,81].

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PDCD1LG2 amplification, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-1, PD-L1, or PD-L2 antibodies. The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses in several cancer types, including melanoma, NSCLC, renal cell carcinoma[101-109], and Hodgkin lymphoma, which harbors frequent PD-L2 copy number gains[77,110]. The PD-L1 antibody atezolizumab does not block interaction between PD-1 and PD-L2; however, multiple clinical studies with atezolizumab have reported an association between increased PD-L2 expression and response or improved overall survival in multiple solid tumor types, thereby suggesting that PD-L2 overexpression may serve as a biomarker of response[63-64,111]. Additionally, JAK2 has been reported as important for PD-L2 expression in Hodgkin lymphoma and PMBCL cell lines, and JAK2 inhibition has been reported to decrease PD-L2 transcript accumulation in preclinical studies[81-82]. Therefore, JAK2 inhibitors may also be relevant for a patient with PD-L2 amplification. Ruxolitinib is a kinase inhibitor that targets JAK1 and JAK2 and is approved to treat intermediate or high-risk myelofibrosis[112].

FREQUENCY & PROGNOSIS

One genomic study of cervical cancer identified focal amplification of chromosomal region 9p24.1, which includes PDCD1LG2, in 21% of cases[85]. Another study reported co-amplification of CD274 and PDCD1LG2 in 23% (11/48) of cervical squamous cell carcinomas (SCC) cases[86]. A study found PD-L2 expression in 29% (33/115) of cervical carcinomas[87]. The prognostic impact of PDCD1LG2 alterations or PD-L2 expression in the context of cervical cancer has not been extensively investigated in the literature (PubMed, Sep 2022).

FINDING SUMMARY

PDCD1LG2 encodes the programmed cell death 1 ligand 2 (PD-L2), also known as CD273, PD-L2, and B7-DC, which is essential for T-cell proliferation and interferon production. PD-1 signaling, which can be stimulated by PD-L2, results in 'T-cell exhaustion', a temporary inhibition of activation and proliferation that can be reversed on removal of the PD-1 signal[94-95]. Amplification of PDCD1LG2 and the adjacent locus CD274, encoding PD-L1, has been reported in 29% of primary mediastinal B-cell lymphoma (PMBCL) cases, and PDCD1LG2 copy number gain has been reported to correlate with increased PD-L2 protein expression as determined by immunohistochemistry[113-114].

GENE
MCL1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to target MCL1 amplification, but MCL1 inhibitors including AMG 176, AMG 397, AZD5991, and S64315 (MIK665) are in early clinical development[115-118]. Limited preclinical data suggest that MCL1 expression alone may not be predictive of sensitivity to MCL1 inhibitors, but BH3 profiling may be a better predictor of MCL1 dependence[116,118-120]. Clinical and preclinical data indicate that increased MCL1 expression may be associated with resistance to BCL2-targeted agents such as venetoclax, navitoclax, or ABT-737[121-128]. In one study, amplification of the genomic locus containing MCL1 was acquired upon disease progression in patients with multiple myeloma treated with venetoclax[129]. Combined inhibition of MCL1 and BCL2 may be more effective[116-118,130-131]. Indirect approaches using therapeutic agents that reduce MCL1 expression are also being investigated[132]. Preclinical studies demonstrate that investigational cyclin-dependent kinase inhibitors targeting CDK9, such as dinaciclib, alvocidib, and voruciclib, suppress gene transcription, reduce MCL1 expression levels, and synergize with BCL2 inhibitors to induce apoptosis[133-140]. Preclinical studies in multiple types of cancer cells have also shown that the multikinase inhibitor sorafenib indirectly downregulates MCL1 and cooperates with BCL2-targeting agents[141-144], and a heavily pretreated patient with metastatic triple-negative breast cancer (TNBC) and MCL1 gene amplification responded to sorafenib in combination with several other therapies[145]. Preclinical studies of patient-derived tumor cells suggest that increased MCL1 levels may confer resistance to antitubulin therapies such as paclitaxel[146], and MCL1 amplification was reported to be more frequent in patients with TNBC and primary resistance to neoadjuvant chemotherapy[147].

FREQUENCY & PROGNOSIS

MCL1 amplification has been reported at the highest incidence in lung adenocarcinoma (16%)[148], breast invasive carcinoma (15%)[149], hepatocellular carcinoma (15%), and bladder urothelial carcinoma (13%)[150] and at lower frequencies in other solid tumor types (cBioPortal, 2023)[151-152]. MCL1 mutations have been reported in fewer than 1% of solid and hematologic cancers (COSMIC, 2023)[153]. In patients with NSCLC, MCL1 amplification was significantly associated with shorter overall survival (hazard ratio 1.39)[154]; high MCL1 protein expression alone was not prognostic in NSCLC[155-157], whereas overexpression of both MCL1 and MYC was linked with poor survival[158]. High MCL1 expression has also been associated with poor prognosis in ovarian[159-160] and colorectal[161] cancers. The prognostic significance of MCL1 expression in breast cancer is not clear[162-163].

FINDING SUMMARY

MCL1 (myeloid cell leukemia 1) encodes a member of the BCL2 family that regulates apoptosis[164]. Focal amplification of MCL1 has been reported in lung, breast, and other cancer types, and the survival of cells with MCL1 amplification is dependent on MCL1 expression[165]. In non-small cell lung cancer (NSCLC), MCL1 amplification was significantly associated with increased MCL1 mRNA expression[154]. Although several MCL1 phosphorylation site mutations have been characterized[166], cancer-associated MCL1 mutations have not been reported (PubMed, 2023).

GENE
MYCL1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies to address alterations in MYCL1.

FREQUENCY & PROGNOSIS

MYCL1 amplification has been reported in a variety of cancer types, including Merkel cell carcinoma (9/23, 39%)[167], prostate cancer (35%)[168-169], ovarian carcinoma (16%)[170], medulloblastoma (3-15%)[171-172], small cell lung cancer (3-8%)[173-174], lung adenocarcinoma (7%)[175], esophageal squamous cell carcinoma (SCC, 3%)[176], cervical SCC (2%)[177], urothelial carcinoma (2%)[178], nasopharyngeal carcinoma (5/8, 62.5%)[179], as well as in a case of hepatocellular carcinoma (HCC)[180]. MYCL1 amplification was not prognostic in prostate cancer in one study[168]. MYCL1 overexpression has been noted in ovarian cancer[170]; Merkel cell carcinoma[167]; testicular germ cell tumors[181]; and gastric cancer, where MYCL1 overexpression is a negative prognostic marker[182]. MYCL1 is a microsatellite marker, and allelic loss is a negative prognostic factor in colorectal adenocarcinoma[183]. Loss of heterozygosity (LOH) of MYCL1 has been reported in 50% of recurrent and 37% of non-recurrent non-small cell lung cancer[184], as well as in 29% of HCCs in one study[185].

FINDING SUMMARY

MYCL1 encodes a protein that regulates transcription of genes involved in cell proliferation, differentiation, and apoptosis[186]. MYCL1 overexpression has been correlated with MYCL1 amplification in ovarian cancer[170] and Merkel cell carcinoma[167].

GENE
NOTCH2

ALTERATION
rearrangement exon 25

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH2 signaling have been developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[187], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI). In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[188]. GS inhibitors would not be relevant for alterations such as observed here, which are expected to be activating and GS-independent.

FREQUENCY & PROGNOSIS

NOTCH2 rearrangement was not found in any of the 298 samples analyzed in the Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma TCGA dataset (cBioPortal, Mar 2022)[151-152]. Published data investigating the prognostic implications of NOTCH2 alteration in cervical cancer are limited (PubMed, Aug 2022).

FINDING SUMMARY

NOTCH2 encodes a member of the NOTCH family of receptors, which play a role in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves gamma-secretase (GS) cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[189-190]. Depending on cellular context, NOTCH2 can act as either a tumor suppressor or an oncogene[191-195]. NOTCH2 rearrangements and fusions that result in expression of the NOTCH2 intracellular domain (amino acids 1699-2471) without the transmembrane domain (amino acids 1678-1698) are predicted to result in GS-independent activation of NOTCH signaling[196]. Similar rearrangements leading to the fusion of SEC22B exon 1 to NOTCH2 exons 27-34 have previously been reported in breast cancer[196] and in chronic lymphocytic leukemia[197] and have been shown to be GS-inhibitor insensitive[196]. Such rearrangements, as observed here, are predicted to be activating.

GENE
PRKCI

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In preclinical studies, the PKCi inhibitor aurothiomalate has been shown to have anti-tumorigenic effects in lung cancer and rhabdomyosarcoma cells[198-200]. A Phase 1 escalation trial of aurothiomalate in patients with advanced lung, ovarian, or pancreatic cancer reported 2/11 enrolled patients achieving stable disease[201]. Other PKCi inhibitors with improved PKCi selectivity, such as CRT0066854 and ICA-1, are in preclinical development[202-203]. In preclinical models, PKCi activation has been reported to promote hedgehog signaling[204] as well as RAS signaling and to require the RAC1-MEK-ERK pathway for tumorigenesis[205-208]. Therefore, MEK inhibitors may be beneficial for a patient with PRKCI amplification. MEK inhibitors are in clinical trials in multiple cancer types. The MEK inhibitors cobimetinib and trametinib are approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations and are being studied in clinical trials in multiple cancer types[209-210].

FREQUENCY & PROGNOSIS

PRKCI has been reported to be frequently amplified in lung SCC, ovarian cancer, and esophageal SCC[204,211-212]. PRKCI amplification and/or protein overexpression has been associated with inferior patient prognosis and/or adverse clinicopathological features in esophageal SCC, cholangiocarcinoma, lung, breast, pancreatic, gastric, ovarian, and brain cancers[205-206,211-216]. In preclinical studies, genetic inhibition of PKCi expression has been shown to have anti-tumorigenic effects in xenografted and/or cultured cells of alveolar rhabdomyosarcoma, non-small cell lung cancer, glioma, and pancreatic, ovarian, and colon carcinoma[198-200,206-207,212-213].

FINDING SUMMARY

PRKCI encodes protein kinase C iota (PKCi), which has been reported to play roles in heart and spinal cord development[217-218]. In esophageal squamous cell carcinoma (SCC), PRKCI amplification strongly correlates with PKCi protein overexpression[211].

Dostarlimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

Activation of PDCD1LG2 may lead to overexpression of PD-L2 and may confer sensitivity to PD-1 inhibitors such as dostarlimab. CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as dostarlimab based on clinical evidence in multiple solid tumor types[219-222] .

SUPPORTING DATA

Clinical data on the efficacy of dostarlimab for the treatment of cervical cancer are limited (PubMed, Sep 2022). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[219,221,223] . 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[221,224] .

Pembrolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. Treatment with pembrolizumab has resulted in a lasting CR in a patient with CD274-amplified DLBCL[225] and in a lasting PR in a patient with CD274-amplified cancer of unknown primary[73]. PD-L1 expression is associated with significantly prolonged median OS for patients with EGFR/ALK wildtype advanced NSCLC treated with pembrolizumab compared with chemotherapy[226-228] . One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and PFS (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[229]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[230].

SUPPORTING DATA

In the Phase 3 placebo-controlled KEYNOTE-826 study for recurrent or metastatic (R/M) cervical cancer, addition of pembrolizumab to frontline platinum-based chemotherapy with or without bevacizumab significantly improved the median PFS (10.4 vs. 8.2 months, HR=0.65) and 24-month OS rates (50.4% vs. 40.4%, HR=0.67); benefit from pembrolizumab was seen in patients with PD-L1-positive tumors (either CPS ≥ 1 or CPS ≥ 10) and in patients with or without concomitant bevacizumab[231]. For patients with previously treated R/M cervical cancer in the Phase 2 KEYNOTE-158 study, single-agent pembrolizumab elicited an ORR of 14.3% and a DCR of 30.6% (5 CRs, 9 PRs, 16 SDs), a median PFS of 2.1 months, and a median OS of 9.3 months; objective responses were observed only in PD-L1-positive (CPS ≥ 1) patients[232-233] . Similar results were observed in an earlier phase study[234] and a retrospective case series[235]. Combination of pembrolizumab with the TF-targeting antibody-drug conjugate tisotumab vedotin elicited an ORR of 38% (2 CRs, 11 PRs) and a median PFS of 5.6 months for patients with previously treated R/M cervical cancer in the Phase 1b/2 ENGOT-Cx8 study[236].

Atezolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangements, that lead to overexpression of PD-L1 may predict sensitivity to atezolizumab based on clinical evidence in multiple solid tumor types[63,111,237] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to anti-PD-L1 inhibitors such as atezolizumab. Although atezolizumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to atezolizumab[63,111,237] .

SUPPORTING DATA

In a Phase 2 open-label study of atezolizumab for advanced solid cancers, an ORR of 15% (4/27), median PFS (mPFS) of 4.1 months, and median OS (mOS) of 14.8 months was reported for patients with previously treated cervical cancer[238]. A Phase 2 basket study of the anti-fibroblast activation protein-alpha simlukafusp alfa combined with atezolizumab reported an ORR of 27% (12/44) and median duration of response of 13.3 months for patients with recurrent or metastatic cervical cancer[239]. A Phase 2 trial combining atezolizumab with bevacizumab for patients with advanced cervical cancer reported only 20% (2/10) unconfirmed PRs as a best response, mPFS of 2.9 months, and mOS of 8.9 months[240].

Avelumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as avelumab based on clinical evidence in multiple solid tumor types[63,111,237,241-244] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as avelumab. Although avelumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[63,111,237] .

SUPPORTING DATA

Clinical data on the efficacy of avelumab for the treatment of cervical cancer are limited (PubMed, Oct 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)[243], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[245], urothelial carcinoma[246], mesothelioma[247], ovarian carcinoma[241], and breast cancer[242], and from avelumab combined with axitinib in renal cell carcinoma[248]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved ORR, PFS, or OS in NSCLC in the first-line setting and in ovarian and breast cancer[241-243] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[249-251] .

Cemiplimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s). In multiple cancer types, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as improved clinical benefit in response to anti-PD-1 immunotherapies[77,110,228-230,252-254] and may predict sensitivity to cemiplimab.

SUPPORTING DATA

In the Phase 3 EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study for patients with recurrent or metastatic cervical cancer and prior platinum-based treatment, second-line cemiplimab elicited improved median OS (mOS) compared with the investigator's choice of chemotherapy (12.0 vs. 8.5 months, HR=0.69), with benefit seen in patients with squamous cell carcinoma (11.1 vs. 8.8 months, HR=0.73) or adenocarcinoma (13.3 vs. 7.0 months, HR=0.56) histology; biomarker analysis reported improved median OS from cemiplimab over chemotherapy for patients whose tumors were PD-L1-positive (TC ≥1%) (13.9 vs. 9.3 mOS, HR=0.70) but not for patients whose tumors were PD-L1-negative (TC <1%) (7.7 vs. 6.7 mOS, HR = 0.98)[255]. In the same setting, cemiplimab treatment as monotherapy or in combination with hypofractionated radiotherapy achieved an ORR of 10% (2/20 CRs) and an mOS of 8.0-10.3 months in a Phase 1 trial[256].

Durvalumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as durvalumab based on clinical evidence in multiple solid tumor types[63,72,111,237,241-244,257-261] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as durvalumab. Although durvalumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[63,111,237] .

SUPPORTING DATA

Clinical data on the efficacy of durvalumab for the treatment of cervical cancer are limited (PubMed, Oct 2022). A Phase 2 trial for patients with recurrent or metastatic HPV-associated cancers reported responses (1 CR and 3 PR) for patients with squamous cell carcinoma of the cervix (1), anus (2), or penis (1) following combination treatment with durvalumab and a DNA vaccine MEDI0457[262]. Single-agent durvalumab has demonstrated efficacy in non-small cell lung cancer[260-261] , and head and neck squamous cell carcinoma[258,263] . 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[264-265] . 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[266]. 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[267] and in patients with BRCA-wild-type breast or gynecological cancer[268]. 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[269]. Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680[270], the CXCR2 antagonist AZD5069[271], or the ATR inhibitor AZD6738[272]. 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[273].

Nivolumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to nivolumab. In various advanced solid tumors, including melanoma, lung, kidney, prostate, and colorectal cancer, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as with objective response to nivolumab[230,254] .

SUPPORTING DATA

A Phase 2 study of nivolumab for treating patients with PD-L1-positive recurrent cervical cancer previously treated with chemotherapy reported an ORR of 4% (1/25), median PFS of 3.5 months, and median OS of 14.5 months[274]. The CheckMate 358 Phase 1/2 trial of single agent nivolumab reported a 26% (5/19, 3 CR) ORR, a 68% (13/19) DCR, a median PFS of 5.1 months, and a median OS of 21.6 months for patients with previously treated cervical squamous cell carcinoma[275-276] . In another study, 22% (2/9) patients with cervical cancer achieved a response to nivolumab or pembrolizumab, with 0% (0/6) patients with 3 or more lines of prior chemotherapy achieving a response[277]. A patient with neuroendocrine cervical cancer that exhibited high tumor mutational burden (TMB) achieved a response to nivolumab and radiation[278]. A patient with recurrent metastatic PD-L1-negative small cell neuroendocrine cervical cancer achieved a CR to nivolumab monotherapy, which was maintained 4 months after nivolumab discontinuation[279].

Nivolumab + Ipilimumab

Assay findings association

CD274 (PD-L1)
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence for PD-L1 overexpression across various solid tumor types, alterations that lead to activation of CD274 may predict sensitivity to combination nivolumab and ipilimumab[31,75,103,264,280] .

SUPPORTING DATA

The cervical cancer cohort of the Phase 1/2 CheckMate 358 trial of combination nivolumab and ipilimumab for patients with virus-associated cancers reported an ORR of 31-38%, median PFS of 3.8-5.8 months, and median OS of 15.2-20.9 months across dosage regimens; ORR was 39-41% in the first-line setting and 26-35% in second-line or higher settings[276]. A patient with heavily pretreated PD-1-negative small cell neuroendocrine cervical cancer achieved a CR to nivolumab combined with ipilimumab lasting >1 year[281]. A case study of a patient with microsatellite instability-high (MSI-H) and tumor mutational burden-high (TMB-High) cervical squamous cell carcinoma who was resistant to pembrolizumab experienced a 2-year durable response to combination nivolumab and ipilimumab[282]. Combination treatment with nivolumab plus the CTLA-4 inhibitor ipilimumab has achieved efficacy in melanoma (up to 61% ORR; median OS [mOS] >60 months for the combination vs. 37 months for nivolumab monotherapy)[104,283-285] , non-small cell lung cancer (NSCLC) (17 months mOS)[286], microsatellite instability-high (MSI-H) colorectal cancer (CRC) (71% ORR [first-line] and 65% ORR [second-line])[287-289] , MSI-H gastric, gastroesophageal junction, and esophageal adenocarcinoma (70% ORR)[290], mismatch repair-deficient (dMMR) and/or MSI-H gastric and gastroesophageal adenocarcinoma (59% [17/29] pathological CR)[291], renal cell carcinoma (RCC) (42% ORR)[75,292] , small cell lung cancer (SCLC) (19-25% ORR)[247,293] , urothelial carcinoma (38% ORR in unselected patients; 58% ORR in patients with ≥1% tumor PD-L1 expression)[294], and other solid tumors.

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

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

GENE
CD274 (PD-L1)

ALTERATION
amplification

RATIONALE
CD274 (PD-L1) amplification or rearrangements that disrupt the 3' UTR may promote PD-1 signaling and inhibit the antitumor immune response. Antibodies that block the interaction of PD-L1 and PD-1 (alone or in combination with anti-CTLA-4) may therefore be beneficial to release the antitumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L1 expression.

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

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT02628067

PHASE 2

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

TARGETS
PD-1

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

NCT05007106

PHASE 2

MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005)

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

LOCATIONS: Taoyuan (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Seoul (Korea, Republic of), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Alaska, Adana (Turkey)

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), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia)

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), Barcelona (Spain), Madrid (Spain), California, Texas

NCT03829501

PHASE 1/2

Safety and Efficacy of KY1044 and Atezolizumab in Advanced Cancer

TARGETS
ICOS, PD-L1

LOCATIONS: Taipei (Taiwan), Napoli (Italy), Milano (Italy), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Tennessee, Florida

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

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), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy)

NCT04282018

PHASE 1/2

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

TARGETS
PI3K-delta, PD-1, BTK

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

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

RATIONALE
PDCD1LG2 (PD-L2) amplification may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L2 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L2 expression.

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

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT02628067

PHASE 2

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

TARGETS
PD-1

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

NCT05007106

PHASE 2

MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005)

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

LOCATIONS: Taoyuan (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Seoul (Korea, Republic of), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Alaska, Adana (Turkey)

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), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia)

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), Barcelona (Spain), Madrid (Spain), California, Texas

NCT03829501

PHASE 1/2

Safety and Efficacy of KY1044 and Atezolizumab in Advanced Cancer

TARGETS
ICOS, PD-L1

LOCATIONS: Taipei (Taiwan), Napoli (Italy), Milano (Italy), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Tennessee, Florida

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

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), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy)

NCT04282018

PHASE 1/2

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

TARGETS
PI3K-delta, PD-1, BTK

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

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.

ATM
L695M

CASP8
amplification

CD22
amplification

CD79B
amplification

CEBPA
amplification

EP300
amplification

GNA13
amplification

IRF2
N284S

MPL
amplification

NBN
rearrangement

NOTCH2
amplification

PRKAR1A
amplification

RET
V388I

SDHA
I247V

SGK1
amplification

SOX9
amplification

ZNF703
L63H

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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 fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

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

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.4.0

The median exon coverage for this sample is 941x

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