FOUNDATIONONE®CDx

MAX Lab

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

CCND1 amplification
CHEK2 loss exons 3-15
ACVR1B loss
FGF19 amplification
TP53 A159P

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 6)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 2 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)**
CCND1 - amplification	none	none
6 Trials see p. 6		
CHEK2 - loss exons 3-15	none	none
10 Trials see p. 8		

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.

ACVR1B - loss .... p. 4
FGF19 - amplification .... p. 4
TP53 - A159P .... p. 5

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

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-H was not detected in a study of 122 hepatocellular (HCC) samples[6], although smaller studies have reported MSI in 0-18% of tumors[7-11], and MSI at some level has been detected in a subset of HCC tumors[6]. The prognostic significance of MSI in HCC has not been determined (PubMed, Jun 2022).

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[12]. 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[12-14]. 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[15-17]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[12,14,16-17].

BIOMARKER

Tumor Mutational Burden

RESULT
2 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[18-20], anti-PD-1 therapies[18-21], and combination nivolumab and ipilimumab[22-27]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[18-21,28-32]. 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[28]; similar findings were observed in the KEYNOTE 028 and 012 trials[21]. 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)[32]. 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[33]. 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[31]. 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[34] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[19].

FREQUENCY & PROGNOSIS

Hepatocellular carcinoma (HCC) harbors a median TMB of 3.6 mutations per megabase (muts/Mb), and 1% of cases have high TMB (>20 muts/Mb)[35]. In an analysis of the TCGA Liver HCC dataset, high TMB was associated with reduced PFS and OS[36]. A retrospective study of 128 patients with HCC who underwent curative resection reported decreased recurrence-free survival for patients with high TMB (>4.8 Muts/Mb) compared to those with low TMB (≤4.8 Muts/Mb) measured in tissue samples[37].

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[38-39] and cigarette smoke in lung cancer[40-41], treatment with temozolomide-based chemotherapy in glioma[42-43], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[44-48], and microsatellite instability (MSI)[44,47-48]. 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[19-20,28].

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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[49-54], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[53,55]. 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[56]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[56]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[57].

FREQUENCY & PROGNOSIS

CCND1 amplification has been reported in 5-7% of hepatocellular carcinomas (HCC) in several studies (cBioPortal, Feb 2023)[58-59]. Published data investigating the prognostic implications of CCND1 alterations in HCC are limited (PubMed, Feb 2023).

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[60] and may lead to excessive proliferation[61-62].

GENE
CHEK2

ALTERATION
loss exons 3-15

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors[63-65]. Clinical benefit has been observed for patients with ovarian[66] and testicular[67] cancers treated with PARP inhibitors. In a study of patients with metastatic breast cancer, 8 patients with CHEK2 mutation did not respond to olaparib treatment[68]. One study of patients with breast cancer reported that carriers of the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy[69], whereas another study found that those who carry CHEK2 mutations have a lower frequency of objective clinical responses to neoadjuvant therapy[70]. A third study reported that the CHEK2 1100delC mutation is not associated with differential efficacy of chemotherapy and endocrine therapy in patients with metastatic breast cancer[71].

FREQUENCY & PROGNOSIS

Somatic CHEK2 mutations have been reported in 0-3% of various solid tumors, with the highest incidence reported in prostate, brain, endometrial, urothelial, and skin tumors (COSMIC, Jan 2023)[72]. In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors as well as bilateral disease[73]. A study reported that a polymorphism in CHEK2 was associated with worse survival of patients with GBM, but this association lost significance after adjusting for other prognostic factors[74-75]. Another study in prostate cancer reported that CHEK2 expression is decreased in higher grade tumors and that CHEK2 is a tumor suppressor that decreases the growth of prostate cancer cells and regulates androgen receptor signaling[76].

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor[77-80]. Alterations such as seen here may disrupt CHEK2 function or expression[81-91].

POTENTIAL GERMLINE IMPLICATIONS

Germline CHEK2 mutation has been associated with cancer susceptibility of low to moderate penetrance, especially in hereditary breast cancer[92]. CHEK2 germline mutation has been identified in approximately 2.5% of familial or high-risk breast cancer cases[93-94]. Although heterozygous germline CHEK2 mutation increases breast cancer risk two- to three-fold, it is not associated with younger age at diagnosis[94-95]. In the appropriate clinical context, germline testing of CHEK2 is recommended.

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GENE

ACVR1B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to address genomic alterations in ACVR1B. Several ALK4 inhibitors are in development[96-99], and inhibitors of Activin A, a ligand for ALK4 and other ALK-family receptors, are in clinical trials[100]. However, further study is required to delineate the respective oncogenic and tumor-suppressive functions of ALK4 and to determine any associations between genomic alterations in ACVR1B and the potential clinical benefit of ALK4 signaling inhibitors.

FREQUENCY & PROGNOSIS

Deletion or loss of heterozygosity of ACVR1B has been predominantly reported for patients with pancreatic cancer (21-34%)[101-102] and has been associated with numerically shorter PFS and OS (p=0.89 and p=0.66)[102], as well as the onset of pancreatic cancer in preclinical studies[103]. By contrast, lower rates of ACVR1B alterations have been reported in other cancers, with highest frequencies of up to 5% reported in colorectal, endometrial, and small bowel adenocarcinoma samples[104-106], whereas amplification has been mainly reported in urothelial carcinoma (3.1%) samples[107]. One study reported significant high expression of ACVR1B in gastric tumor samples compared with non-cancerous tissue, which was significantly associated with advanced tumor stages and poor patient outcomes[108]. Mutations in ACVR1B have been identified in 6.3% (2/32) of patients with small cell lung cancer, which were associated with higher levels of neuron-specific enolase (p=0.013)[109]. Significant low expression of ACVR1B has been reported in glioma tumor samples relative to non-cancerous tissues[110].

FINDING SUMMARY

ACVR1B encodes ALK4, also known as activin receptor 1B, which mediates TGF-beta signaling, including for ligands such as Activin and Nodal, through regulation of SMAD transcription factors[101,111-113]. ACVR1B is reported to have potential oncogenic roles in some cancer types, such as prostate cancer[114], and potential tumor-suppressive functions in others, such as thyroid[115] and pancreatic[101-102] cancers; however, one preclinical study suggested that signaling through ALK4 may promote pancreatic cancer stem cell functions[112]. A single-nucleotide polymorphism in ACVR1B was associated with risk of lung cancer in never smokers exposed to second-hand smoke[116].

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)[117]. 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[118]. 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[119]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[120], 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[121]. 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[122].

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%)[123-125]. FGF19 mutations are rare in solid tumors[123]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[126-127], and in prostate cancer following radical prostatectomy[128]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[129] and lung SCC[130].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[131-132]. 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[133]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[134], lung squamous cell carcinoma[130,135], and head and neck squamous cell carcinoma (HNSCC)[129], but was not observed in other cancers[121,136].

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GENE

TP53

ALTERATION
A159P

HGVS VARIANT
NM_000546.4: c.475G>C (p.A159P)

VARIANT CHROMOSOMAL POSITION
chr17:7578455

VARIANT ALLELE FREQUENCY (% VAF)
87.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[137-140] or p53 gene therapy such as SGT53[141-145]. 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[146]. 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[147]. 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[148]. 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[149]. 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[150]. 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[151]. 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[152]. 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[145]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[153]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[154].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 30-31% of hepatocellular carcinoma (HCC) cases[155-156]. TP53 has been reported to be the most frequently mutated tumor suppressor in HCC, with mutations identified in 16-35% of cases[134,157-158]. Significantly higher rates of TP53 mutation have been reported in HCC associated with Hepatitis B or Hepatitis C infections compared to other types of HCC[159-161]. Expression of p53 has been variously identified in 35-96% of HCC cases[157,162]. Studies have reported that patients with hepatocellular carcinoma harboring TP53 mutations and/or p53 upregulation experienced significantly shorter recurrence-free survival and OS[157,162-164].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[165]. Alterations such as seen here may disrupt TP53 function or expression[166-170].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[171-173], including sarcomas[174-175]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[176] to 1:20,000[175]. 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[177]. 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[178-183]. 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[178-179]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[184]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[182,185-186]. 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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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

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

NCT05252416

PHASE 1/2

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

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, New York, Illinois, Virginia, Arkansas, Florida, Texas

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NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

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GENE
CHEK2

ALTERATION
loss exons 3-15

RATIONALE
On the basis of clinical evidence in prostate and other solid cancers, CHEK2 loss or inactivation may confer sensitivity to PARP inhibitors.

NCT04123366
PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Malatya (Turkey), Adana (Turkey), Jerusalem (Israel), Kfar Saba (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Ankara (Turkey), Konya (Turkey)

NCT03742895
PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Adana (Turkey), Jerusalem (Israel), Ramat Gan (Israel), Konya (Turkey), Antalya (Turkey), Istanbul (Turkey), Izmir (Turkey), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Edirne (Turkey)

NCT05035745
PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT02264678
PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Lyon Cedex 08 (France), Villejuif (France), Cambridge (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Coventry (United Kingdom)

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)

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NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Connecticut, New York, Pennsylvania, Tennessee, Oklahoma, Florida, 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: Edmonton (Canada), Saskatoon (Canada), Vancouver (Canada), Kelowna (Canada), Regina (Canada), Montreal (Canada), Ottawa (Canada), Kingston (Canada), Toronto (Canada), London (Canada)

NCT02693535

PHASE 2

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

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

LOCATIONS: Maine, Washington

NCT04992013

PHASE 2

Niraparib in Tumors Metastatic to the CNS

TARGETS
PARP

LOCATIONS: Massachusetts

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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
amplification

BCL6
NM_001706.4: c.234C>G
(p.I78M)
chr3:187449646

ERG
NM_182918.3: c.823C>T
(p.P275S)
chr21:39763629

HNF1A
loss

KDM5A
NM_001042603.1: c.3311A>G
(p.D1104G)
chr12:419036

MED12
NM_005120.2:
c.6348_6359dup
(p.H2116_Q2119dup)
chrX:70361151

NTRK1
NM_002529.3: c.617A>T
(p.D206V)
chr1:156838339

PRKN (PARK2)
NM_004562.2: c.125G>A
(p.R42H)
chr6:162864388

RAD51D
NM_002878.3: c.29C>T
(p.P10L)
chr17:33446604

ROS1
NM_002944.2: c.3139C>A
(p.P1047T)
chr6:117684008

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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)

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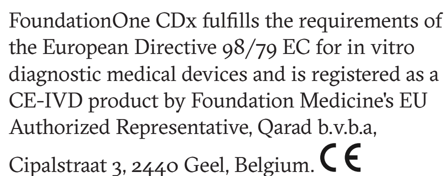

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

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 PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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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

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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) 7.8.0

The median exon coverage for this sample is 875x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Goumard C, et al. Cancer Genomics Proteomics () pmid: 28871000
7. Gross-Goupil M, et al. Int. J. Cancer (2003) pmid: 12640682
8. Zhang SH, et al. World J. Gastroenterol. (2005) pmid: 15918185
9. Chiappini F, et al. Carcinogenesis (2004) pmid: 14656944
10. Salvucci M, et al. Oncogene (1999) pmid: 9926933
11. Wang L, et al. Int. J. Oncol. (2001) pmid: 11494037
12. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
13. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
14. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
15. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
16. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
17. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
18. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
19. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
20. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
21. Cristescu R, et al. Science (2018) pmid: 30309915
22. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
23. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
24. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
25. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
26. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
27. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
28. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
29. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
30. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
31. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
32. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
33. Schenker at al., 2022; AACR Abstract 7845
34. Legrand et al., 2018; ASCO Abstract 12000
35. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
36. Shrestha R, et al. Front Oncol (2018) pmid: 30057891
37. Cai H, et al. J Surg Oncol (2020) pmid: 31995247
38. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
39. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
40. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
41. Rizvi NA, et al. Science (2015) pmid: 25765070
42. Johnson BE, et al. Science (2014) pmid: 24336570
43. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
44. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
45. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
46. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
47. Nature (2012) pmid: 22810696
48. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
49. Morschhauser F, et al. Haematologica (2020) pmid: 32381571
50. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
51. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
52. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
53. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
54. Leonard JP, et al. Blood (2012) pmid: 22383795
55. Dickler MN, et al. Clin. Cancer Res. (2017) pmid: 28533223
56. Clark et al., 2019; AACR Abstract LB-010/2
57. Peguero et al., 2016; ASCO Abstract 2528
58. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
59. Gao J, et al. Sci Signal (2013) pmid: 23550210
60. Elsheikh S, et al. Breast Cancer Res. Treat. (2008) pmid: 17653856
61. Fu M, et al. Endocrinology (2004) pmid: 15331580
62. Takahashi-Yanaga F, et al. Cell. Signal. (2008) pmid: 18023328
63. Abida W, et al. Clin. Cancer Res. (2020) pmid: 32086346
64. Mateo J, et al. Lancet Oncol. (2019) pmid: 31806540
65. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
66. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
67. Gruber et al., 2019; ASCO Abstract 3006
68. Tung NM, et al. J Clin Oncol (2020) pmid: 33119476
69. Liu Y, et al. BMC Cancer (2015) pmid: 25884806
70. Pfeifer W, et al. Breast Cancer Res. Treat. (2014) pmid: 25414026
71. Kriege M, et al. J. Cancer Res. Clin. Oncol. (2015) pmid: 25958056
72. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
73. Kilpivaara O, et al. Int. J. Cancer (2005) pmid: 15472904
74. Simon M, et al. Neurosurgery (2006) pmid: 17016233
75. Dong YS, et al. Tumour Biol. (2014) pmid: 24532427
76. Ta HQ, et al. Cancer Res. (2015) pmid: 26573794
77. Tomlinson IP, et al. Mutagenesis (2012) pmid: 22294770
78. Xu HP, et al. Nucleic Acids Res. (1990) pmid: 2205842
79. van der Groep P, et al. Cell Oncol (Dordr) (2011) pmid: 21336636
80. Schutte M, et al. Am. J. Hum. Genet. (2003) pmid: 12610780
81. Xu X, et al. Mol. Cell. Biol. (2002) pmid: 12024051
82. Lee CH, et al. J. Biol. Chem. (2001) pmid: 11390408
83. Schwarz JK, et al. Mol. Cancer Res. (2003) pmid: 12805407
84. Ng CP, et al. J. Biol. Chem. (2004) pmid: 14681223
85. Matsuoka S, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10973490
86. Zhou BB, et al. J. Biol. Chem. (2000) pmid: 10744722
87. Ahn JY, et al. Cancer Res. (2000) pmid: 11085506
88. Melchionna R, et al. Nat. Cell Biol. (2000) pmid: 11025670
89. Yoda A, et al. J. Biol. Chem. (2006) pmid: 16798742
90. Chehab NH, et al. Genes Dev. (2000) pmid: 10673500
91. Lee SB, et al. Cancer Res. (2001) pmid: 11719428
92. Mahdavi M, et al. J Cell Physiol (2019) pmid: 30552672
93. Kleiblová P, et al. Klin Onkol (2019) pmid: 31409080
94. Hauke J, et al. Cancer Med (2018) pmid: 29522266
95. Lu HM, et al. JAMA Oncol (2019) pmid: 30128536
96. Inman GJ, et al. Mol. Pharmacol. (2002) pmid: 12065756
97. DaCosta Byfield S, et al. Mol. Pharmacol. (2004) pmid: 14978253
98. Jin CH, et al. J. Med. Chem. (2014) pmid: 24786585
99. Hanke T, et al. ACS Chem Biol (2020) pmid: 32176847
100. Ries A, et al. Expert Opin Ther Targets (2020) pmid: 32700590
101. Su GH, et al. Proc. Natl. Acad. Sci. U.S.A. (2001) pmid: 11248065
102. Togashi Y, et al. Mol. Cancer (2014) pmid: 24886203
103. Qiu W, et al. Gastroenterology (2016) pmid: 26408346
104. Giannakis M, et al. Cell Rep (2016) pmid: 27149842
105. Dou Y, et al. Cell (2020) pmid: 32059776
106. Hänninen UA, et al. PLoS Genet (2018) pmid: 29522538
107. Nature (2014) pmid: 24476821
108. Liu K, et al. Oncogene (2020) pmid: 32066878
109. Jin W, et al. Biomed Res Int (2021) pmid: 33880365
110. Song C, et al. Biomed Pharmacother (2018) pmid: 29278854
111. Vo BT, et al. Prostate (2011) pmid: 21557273
112. Lonardo E, et al. Cell Stem Cell (2011) pmid: 22056140
113. Tykwinska K, et al. PLoS ONE (2013) pmid: 23950971
114. Nomura M, et al. Biochem. Biophys. Res. Commun. (2013) pmid: 23159635
115. Schulte KM, et al. Thyroid (2001) pmid: 11272093
116. Spitz MR, et al. Cancer Discov (2011) pmid: 22586632
117. Kim RD, et al. Cancer Discov (2019) pmid: 31575541
118. Chan et al., 2017; AACR Abstract CT106
119. Macarulla et al., 2021; ASCO Abstract 4090
120. Kaibori M, et al. Oncotarget (2016) pmid: 27384874
121. Kanzaki H, et al. Sci Rep (2021) pmid: 33674622
122. Dumbrava EI, et al. JCO Precis Oncol (2018) pmid: 31123723
123. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
124. Nature (2012) pmid: 22960745
125. Robertson AG, et al. Cell (2017) pmid: 28988769
126. Miura S, et al. BMC Cancer (2012) pmid: 22309595
127. Kang HJ, et al. Liver Cancer (2019) pmid: 30815392
128. Nagamatsu H, et al. Prostate (2015) pmid: 25854696
129. Gao L, et al. Oncogene (2019) pmid: 30518874
130. Li F, et al. Oncogene (2020) pmid: 32111983
131. Xie MH, et al. Cytokine (1999) pmid: 10525310
132. Hagel M, et al. Cancer Discov (2015) pmid: 25776529
133. Int. J. Oncol. (2002) pmid: 12429977
134. Kan Z, et al. Genome Res. (2013) pmid: 23788652
135. Caruso S, et al. Gastroenterology (2019) pmid: 31063779
136. Sawey ET, et al. Cancer Cell (2011) pmid: 21397858
137. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
138. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
139. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
140. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
141. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
142. Xu L, et al. Mol. Med. (2001) pmid: 11713371
143. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
144. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
145. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
146. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
147. Moore et al., 2019; ASCO Abstract 5513
148. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
149. Oza et al., 2015; ASCO Abstract 5506
150. Lee J, et al. Cancer Discov (2019) pmid: 31315834
151. Méndez E, et al. Clin. Cancer Res. (2018) pmid:

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29535125
152. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
153. Gourley et al., 2016; ASCO Abstract 5571
154. Park H, et al. ESMO Open (2022) pmid: 36084396
155. Ahn SM, et al. Hepatology (2014) pmid: 24798001
156. Harding JJ, et al. Clin. Cancer Res. (2018) pmid: 30373752
157. Liu J, et al. Eur. J. Cancer (2012) pmid: 22459764
158. Kalinina O, et al. Mutat. Res. (2013) pmid: 23830926
159. Guerrieri F, et al. Semin. Liver Dis. (2013) pmid: 23749671
160. Long J, et al. Oncol. Rep. (2013) pmid: 23624687
161. Tornesello ML, et al. Genomics (2013) pmid: 23583669
162. Kang GH, et al. Gut Liver (2014) pmid: 24516705
163. Ji YN, et al. Tumour Biol. (2014) pmid: 24078450
164. Zhan P, et al. Hepatobiliary Surg Nutr (2014) pmid: 24696834
165. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
166. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
167. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
168. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
169. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
170. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
171. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
172. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
173. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
174. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
175. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
176. Lalloo F, et al. Lancet (2003) pmid: 12672316
177. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
178. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
179. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
180. Xie M, et al. Nat. Med. (2014) pmid: 25326804
181. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
182. Severson EA, et al. Blood (2018) pmid: 29678827
183. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
184. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
185. Chabon JJ, et al. Nature (2020) pmid: 32269342
186. Razavi P, et al. Nat. Med. (2019) pmid: 31768066

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PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)

Patient Result

Tumor Proportion Score (TPS) (%)*

** See tables 1 and 2 for interpretation.*

Electronically signed by: ______________________ Date: ______________

Table 1: TPS Companion Diagnostic Indications

Tumor Indication	PD-L1 Expression Level	Intended Use
Non-Small Cell Lung Cancer (NSCLC)	TPS ≥1%	PD-L1 IHC 22C3 pharmDx™ is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).†
	TPS ≥50%	PD-L1 IHC 22C3 pharmDx™ is indicated as an aid in identifying NSCLC patients for treatment with LIBTAYO® (cemiplimab).‡

† See the KEYTRUDA® product label for specific clinical circumstances guiding PD-L1 testing.

‡ See the LIBTAYO® product label for specific clinical circumstances guiding PD-L1 testing.

Table 2: Other Tumor Types

Tumor Indication	PD-L1 Expression Level	Intended Use
Non-Companion Diagnostic Tumor Type	TPS cut-off criteria for other tumor types have not been defined for this assay by the US FDA.	N/A

Methodology
PD-L1 IHC 22C3 pharmDx™ is a qualitative immunohistochemical assay using mouse monoclonal anti-PD-L1. Clone 22C3 is intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC), cervical cancer, head and neck squamous cell carcinoma (HNSCC), and triple-negative breast cancer (TNBC) tissues using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression in NSCLC is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. This product is intended for in vitro diagnostic use. For additional information, refer to the PD-L1 IHC 22C3 pharmDx™ Package Insert.

Clinical Significance of PD-L1 Protein Expression
Programmed death-ligand 1 (PD-L1), expressed on tumor cells and tumor-infiltrating immunocytes, mediates an immune checkpoint by binding to its receptors, programmed death 1 (PD-1) and B7-1, on activated T cells[1–4]. This checkpoint represses T-cell function and can therefore lead to evasion of anti-tumor immunity. On the basis of extensive clinical evidence in various tumor types, PD-L1-positive tumors are more likely to respond to PD-1/PD-L1 checkpoint inhibitors; however, patients with PD-L1-negative tumors may also derive benefit from these agents[4–14]. Checkpoint inhibitors such as the PD-1 antibodies cemiplimab, nivolumab, and pembrolizumab and the PD-L1 antibodies atezolizumab, avelumab, and durvalumab are US FDA approved to treat various tumor types.

Note
This test has been cleared or approved by the U.S. Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Foundation Medicine, Inc. per Clinical Laboratory Improvement Amendments (CLIA '88) requirements and in accordance with the College of American Pathologists (CAP).

General Limitations

- Immunohistochemical analysis is dependent on the handling and processing of tissue prior to staining; false negative or inconsistent results may be a consequence of pre-analytic variations.
- As with any immunohistochemistry test, a negative result means that the antigen was not detected, not that the antigen was absent in the cells or tissue assayed.
- For additional information and comprehensive list of limitations, refer to the PD-L1 IHC 22C3 pharmDx™ Package Insert.

References

1. Keir, M. E., Butte, M. J., Freeman, G. J. & Sharpe, A. H. PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. 26, 677–704 (2008).
2. Butte, M. J., Keir, M. E., Phamduy, T. B., Sharpe, A. H. & Freeman, G. J. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 27, 111–122 (2007).
3. Ma, W., Gilligan, B. M., Yuan, J. & Li, T. Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. J. Hematol. Oncol. 9, 47 (2016).
4. Herbst, R. S. et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 515, 563–567 (2014).
5. Topalian, S. L., Taube, J. M., Anders, R. A. & Pardoll, D. M. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat. Rev. Cancer. 16, 275–287 (2016).
6. Taube, J. M. et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin. Cancer Res. 20, 5064–5074 (2014).
7. Garon, E. B. et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N. Engl. J. Med. 372, 2018–2028 (2015).
8. Nghiem, P. T. et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N. Engl. J. Med. 374, 2542–2552 (2016).
9. Fehrenbacher, L. et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 387, 1837–1846 (2016).
10. Rosenberg, J. E. et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 387, 1909–1920 (2016).
11. Patel, S. P. & Kurzrock, R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol. Cancer Ther. 14, 847–856 (2015).
12. Mok, T.S.K. et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. doi.org/10.1016/S0140-6736(18)32409-7 (2019).
13. Herbst, R.S. et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 387, 1540–1550 (2016).
14. Sezer, A. et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet. 397, 592–604 (2021).

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