FOUNDATIONONE®HEME

PATIENT	TUMOR TYPE	REPORT DATE
Lin, Mei-Chen	Unknown primary malignant neoplasm	19 Apr 2022
	COUNTRY CODE: TW	ORDERED TEST #: ORD-1336448-02

ABOUT THE TEST FoundationOne® Heme is a comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas.

PATIENT
DISEASE Unknown primary malignant neoplasm
NAME Lin, Mei-Chen
DATE OF BIRTH 30 January 1981
SEX Female
MEDICAL RECORD # 43982770

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 Mouth
SPECIMEN ID S111-07951 A (PF22046)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 23 February 2022
SPECIMEN RECEIVED 04 April 2022

Biomarker Findings

Tumor Mutational Burden - 63 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

MET amplification
ERBB3 V104L
ETV6 inversion intron 5, rearrangement intron 5
FLT4 V160L
HIST1H1D Q182*
KEAP1 E41*
TET2 V1417F
TP53 splice site 375G>T
TRAF3 Q492*

Report Highlights

- Targeted therapies with potential clinical benefit **approved in this patient's tumor type**: Dostarlimab (p. 11), Pembrolizumab (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 18)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***TET2* V1417F** (p. 8)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 63 Muts/Mb	Dostarlimab	Atezolizumab
	Pembrolizumab	Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
		Nivolumab + Ipilimumab
10 Trials *see p. 18*		
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	

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PATIENT
Lin, Mei-Chen

TUMOR TYPE
Unknown primary malignant neoplasm

COUNTRY CODE
TW

REPORT DATE
19 Apr 2022

ORDERED TEST #
ORD-1336448-02

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET **-** amplification	none	Cabozantinib
		Capmatinib
		Crizotinib
6 Trials *see p. 21*		Tepotinib
ERBB3 **-** V104L	none	none
1 Trial *see p. 20*		

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

TET2 **-** V1417F ..... 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.

ETV6 - inversion intron 5, rearrangement intron 5 ..... p. 5
FLT4 - V160L ..... p. 6
HIST1H1D - Q182* ..... p. 6
KEAP1 - E41* ..... p. 7
TET2 - V1417F ..... p. 8
TP53 - splice site 375G>T ..... p. 9
TRAF3 - Q492* ..... p. 10

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

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.

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BIOMARKER

Tumor Mutational Burden

RESULT
63 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[1-4,11]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[1]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[12] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[2]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[4,11]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

High or elevated TMB has been most frequently reported in melanoma (17-42%)[13-15], colorectal cancer (CRC; 8-25%)[16-19], endometrial carcinoma (7-24%)[20-22], intestinal-type stomach adenocarcinoma (20%)[20], and non-small cell lung carcinoma (NSCLC; 8-13%)[23-24] . In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[25], 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 (10.3%) or KRAS (9.4%)[23]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[25-26], several other large studies did find a strong link[27-30]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[18-19] and with microsatellite instability (MSI)[19], which in turn has been reported to correlate with better prognosis[31-38]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[22,39-41] and bladder cancer[42], it is also linked with improved prognosis in patients with these tumor types[22].

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[43-44] and cigarette smoke in lung cancer[45-46], treatment with temozolomide-based chemotherapy in glioma[47-48], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[18,22,49-51], and microsatellite instability (MSI)[18,22,51]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[2-4,11].

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[52-54], including approved therapies nivolumab and pembrolizumab[55]. 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)[56].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)[57-64], colorectal cancers (CRCs; 10-15%)[18,37,54,65-66], and gastric cancers (12-35%)[67-70] and at lower frequencies in many other tumor types, including esophageal[71], small bowel[72-76], hepatobiliary[77-83], prostate[84-86], and urinary tract carcinomas[87-89]. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy[90]. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting[57,60-61,63,91-93]. However, studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[59,62,64,92], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[66]. 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[66,94-95]. 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[65,96-97]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[65-66,95,97].

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GENE
MET

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[98-101], gastroesophageal cancer[102], glioblastoma[103], and carcinoma of unknown primary[104]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[105-106] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[107-109]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[110] and NSCLC[111] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[112-114] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[115] and gastric cancer either alone or in combination with docetaxel[116-117]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[118]. Patients with MET-amplified NSCLC[119] or MET-amplified gastric cancer[120] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab, as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[121]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[122]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[123].

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of MET has been found in several tumor types, with the highest incidences in ovarian serous cystadenocarcinoma (5.5%), esophageal carcinoma (3.4%), stomach adenocarcinoma (3.7%), and lung adenocarcinoma (3.0%) datasets; lower incidences were observed in various other tumor types (cBioPortal, Sep 2021)[124-125]. Overexpression of MET mRNA and protein has been observed in a number of cancers[126-128]. MET amplification has been associated with poor prognosis in gastroesophageal adenocarcinoma, gastric and esophageal cancer[102,129-134]. Increased MET expression has been associated with poor prognosis in cutaneous malignant melanoma[135], gallbladder adenocarcinoma[136], lung large cell neuroendocrine carcinoma[137], and breast cancer[138-140]. The prognostic value of MET amplification or expression in non-small cell lung cancer (NSCLC)[141-148], endometrial carcinoma[149-152] or colon cancer[153-155] have yielded conflicting results, although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival in NSCLC[156].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[157-158]. MET has been reported to be amplified in cancer[125], with amplification positively correlating with protein expression in some cancer types[126-128,142,159] and associating with therapeutic response to MET inhibitors in a variety of cancer types[98-100,102-104,160-161].

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GENE
ERBB3

ALTERATION
V104L

TRANSCRIPT ID
NM_001982

CODING SEQUENCE EFFECT
310G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[162-165]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Preclinical studies support the sensitivity of cells with ERBB3 activating mutations to various anti-ERBB2 agents[164,166-167]. In a Phase 2 study of afatinib in platinum-refractory urothelial cancer, 2 patients with activating ERBB3 mutations but no EGFR or HER2 activating alterations experienced clinical benefit and PFS > 6 months[168]. Other studies in solid tumors have reported mixed efficacy for afatinib for patients with uncharacterized ERBB3 mutations[169-170]. Case studies report clinical benefit from lapatinib combined with either capecitabine[169] or trastuzumab[169,171] for patients with breast cancer harboring activating ERBB3 mutations. However, Phase 2 trials have suggested limited efficacy of other ERBB2-targeting TKIs against ERBB3 mutations, with no objective response to neratinib in any of 16 patients with ERBB3-mutated solid tumors[172] or dacomitinib in either of 2 patients with ERBB3-mutated cutaneous squamous cell carcinoma[173].

FREQUENCY & PROGNOSIS

ERBB3 mutations have been reported with highest incidence in cancers of the meninges (31%), urinary tract (11%), stomach (7.5%), skin (7.2%), endometrium (6.8%), prostate (5.3%), large intestine (5.2%), biliary tract (4.7%), and cervix (4%) and at lower frequencies in other tumor types (COSMIC, Apr 2022)[174]. High expression of ERBB3 mRNA or ERBB3 protein has been found in a number of tumor types, including those of the breast, lung, ovary, stomach, colon, and bladder[175-185]. Elevated ERBB3 expression has been associated with increased disease severity or negative prognostic indicators in glioblastoma[186], gastric cancer[187-188], non-small cell lung cancer[178], and colorectal cancer[189]. ERBB3 amplification in breast cancer has been correlated with reduced disease-free survival, although some studies have found no association with prognosis[190-197]. The data associating ERBB3 expression and invasion and metastasis in urothelial carcinoma were similarly conflicting[198-203].

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[204]. ERBB3 mutations such as observed here have been shown to be activating[164,167,205-206].

GENE
ETV6

ALTERATION
inversion intron 5, rearrangement intron 5

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that address ETV6 mutation or inactivation.

FREQUENCY & PROGNOSIS

ETV6 mutation has been observed in up to 7% of cutaneous squamous cell carcinomas[207], 6% of colorectal adenocarcinomas[208], 5.5% of bladder cancers[209], 4% each of melanomas and endometrial carcinomas, and in lower frequencies in other tumor types cBioPortal, Apr 2022)[124-125]. High ETV6 expression associated with poor prognosis in one study[210], and low ETV6 expression associated with improved OS and disease-free survival in patients with NSCLC[211].

FINDING SUMMARY

ETV6 encodes an ETS family transcription factor required for hematopoiesis. The portion of chromosome 12 that encodes ETV6 is frequently involved in translocation events, and at least 30 fusion partners have been identified to date[212-213]. ETV6 rearrangements have been implicated in various hematopoietic malignancies[214] and have been reported to be pathogenic by a number of different mechanisms including activation of a partner oncogene, ETV6 inactivation, or aberrant transcription factor activity[213]. Alterations such as seen here may disrupt ETV6 function or expression[215-219].

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GENE
FLT4

ALTERATION
V160L

TRANSCRIPT ID
NM_002020

CODING SEQUENCE EFFECT
478G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Based on clinical studies, FLT4 amplification may be associated with sensitivity to kinase inhibitors with activity against VEGFR3 such as axitinib and sorafenib; responses to axitinib have been observed in patients with FLT4-amplified differentiated thyroid carcinoma[220], and responses to sorafenib have been reported in patients with FLT4-amplified angiosarcoma[221]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the TCGA datasets, FLT4 mutation has been reported in 11.6% of cutaneous melanomas, 7.5% of endometrial carcinomas, 5.6% of colorectal adenocarcinomas, 5.5% of stomach adenocarcinomas, and at lower incidence across a range of other tumor types (cBioPortal, Apr 2022)[124-125]. Published data investigating the prognostic implications of FLT4 alterations in solid tumors are generally limited (PubMed, Apr 2022).

FINDING SUMMARY

FLT4 encodes the protein fms-related tyrosine kinase 4, also known as VEGFR-3 (vascular endothelial growth factor receptor 3). Targeting of VEGF receptors has been a major therapeutic strategy in cancer as growth of new blood and lymph vessels is a critical determinant of tumor growth and metastasis[222-223]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
HIST1H1D

ALTERATION
Q182*

TRANSCRIPT ID
NM_005320

CODING SEQUENCE EFFECT
544C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are currently no therapies available to directly address genomic alterations in HISTH1D.

FREQUENCY & PROGNOSIS

Recurrent missense mutations in the genes that encode H1 isoforms B–E, have been reported at high frequencies in B cell lymphomas, including 30–40% of diffuse large B cell lymphomas (DLBCLs), 30% of follicular lymphomas and 50% of Hodgkin lymphomas, and lower frequencies across other tumor types[224-228]. Published data investigating the prognostic implications of HIST1H1D alterations in cancer are limited (PubMed, Apr 2022).

FINDING SUMMARY

HIST1H1D encodes histone H1.3 (H1D), a linker histone that interacts with DNA between nucleosomes and functions in the regulation of gene expression and compaction of chromatin into higher order structures[229-230]. Missense mutations in linker histones affecting the globular and C-terminal domains have been identified in cancer and often correlate with loss of function[230], whereas other alterations are mostly uncharacterized.

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GENE
KEAP1

ALTERATION
E41*

TRANSCRIPT ID
NM_012289

CODING SEQUENCE EFFECT
121G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[231]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[232-233]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[234]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[235]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[236]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[237] or STK11- or KEAP1-mutated tumors (p <0.001)[238] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[239]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[240]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[241-243]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[244]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[244]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[245].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[246]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2022)[174]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[235].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[247]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[248-250]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[249-250].

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GENE
TET2

ALTERATION
V1417F

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
4249G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[124-125]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[251-252]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL 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[253-258]. 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[253-254]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[259]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[257,260-261]. 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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GENE
TP53

ALTERATION
splice site 375G>T

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
375G>T

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[262-265], or p53 gene therapy and immunotherapeutics such as SGT-53[266-270] and ALT-801[271]. 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[272]. 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[273]. 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[274]. 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[275]. 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[116]. 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[276]. 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[277]. 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[270]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[278-279]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[280-281]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[282]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[283]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[284].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[285]. Alterations such as seen here may disrupt TP53 function or expression[286-290].

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[291-293], including sarcomas[294-295]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[296] to 1:20,000[295]. 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[297]. 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[253-258]. 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[253-254]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[259]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[257,260-261]. 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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GENE
TRAF3

ALTERATION
Q492*

TRANSCRIPT ID
NM_003300

CODING SEQUENCE EFFECT
1474C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target TRAF3 inactivation or the activation of the NF-kB pathway, although these are under development. The Bruton's tyrosine kinase inhibitor ibrutinib has been reported to inhibit NF-kB pathway activation in chronic lymphocytic leukemia samples and myeloma cells[298-300]. However, preclinical data in mantle cell lymphoma cells suggest that inactivation of TRAF3 or the related TRAF2 may correlate with insensitivity to ibrutinib and to the PKC inhibitor sotrastaurin[301]. This insensitivity was attributed to activation of alternative NF-kB signaling, which could be inhibited by targeting the kinase NIK (MAP3K14) in preclinical assays[301].

FREQUENCY & PROGNOSIS

TRAF3 mutations have been reported with the highest incidences in the uterine corpus endometrial carcinoma (3.4%), skin cutaneous melanoma (2.7%), cervical squamous cell carcinoma (2.4%), stomach adenocarcinoma (2.3%), and colorectal adenocarcinoma (2.0%) TCGA datasets (cBioPortal, Mar 2022)[124-125]. Published data investigating the prognostic implications of TRAF3 alterations in solid tumors are limited (PubMed, Mar 2022).

FINDING SUMMARY

TRAF3, a member of the TRAF family of adaptor proteins, has E3 ubiquitin ligase activity and is a critical determinant of B-cell survival[302-303]. TRAF3 loss leads to the activation of the NF-kB pathway and is thought to function as a tumor suppressor in a variety of B-cell lineage neoplasms[304-308]. Alterations such as seen here may disrupt TRAF3 function or expression.

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Dostarlimab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[310-312] . 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[310,313] .

Pembrolizumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In the Phase 2 KEYNOTE 158 multi-solid tumor trial, treatment with the PD-1 inhibitor pembrolizumab led to improved ORR for patients with TMB of 10 Muts/Mb or higher compared those with TMB <10 Muts/Mb (28.3% [34/120] vs. 6.5% [41/635])[11]. In the KEYNOTE 028/012 pan-solid tumor trials, a similar improvement in ORR was reported for patients with >103 non-synonymous mutations/exome (~ equivalency >8 Muts/Mb as measured by this assay) compared to those with <103 non-synonymous mutations/exome (30.6% [11/36] vs. 6.5% [5/77])[4]. Pembrolizumab has achieved significant clinical benefit for patients with PD-L1-expressing solid tumors including gastric carcinoma (ORR=22.0%)[314], esophageal carcinoma (ORR=22.0%)[315], endometrial carcinoma (ORR=13.0%)[39,316] , lung carcinoma (median OS=14.9 months)[317], urothelial tract carcinoma (ORR=24.0%)[318], head and neck carcinoma (ORR=12.0–26.0%)[319-322] , breast carcinoma (ORR=16.0-25.0%)[323-324] , cervical squamous cell carcinoma (ORR=12.5%)[325], thyroid carcinoma (ORR=9.0%)[326], and pleural mesothelioma (ORR=24.0%)[327]. In the KEYNOTE-051 Phase 1/2 study of pembrolizumab for the treatment of pediatric patients with advanced cancer, PRs were reported in 8 patients including 2 adrenocortical carcinomas, 2 mesotheliomas, 1 malignant ganglioglioma, 1 epithelioid sarcoma, 1 lymphoepithelial carcinoma, and 1 malignant rhabdoid[328]. Clinical studies have reported responses to pembrolizumab in combination with other immunotherapies such as ipilimumab in recurrent advanced non-small cell lung carcinoma (NSCLC)(ORR=24.0%)[329-330] , and nivolumab in glioma (2/12 PRs, 4/12 SDs)[331]. Clinical benefit has also been achieved with pembrolizumab in combination with chemotherapy for advanced non-squamous NSCLC[332], IDO-1 inhibitor epacadostat for solid tumors[333], HDAC inhibitor entinostat for breast and endometrial cancer[123], bevacizumab for glioblastoma[334], and lenvatinib for patients with advanced endometrial carcinoma that is not MSI-H or dMMR[335].

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Atezolizumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In the prospective Phase 2a MyPathway basket study evaluating atezolizumab for patients with TMB-High solid tumors, patients with TMB ≥16 Muts/Mb achieved improved ORR (38% [16/42] vs. 2.1% [1/48]), DCR (62% [26/42] vs. 23% [11/48]), mPFS (5.7 vs. 1.8 months, HR 0.34), and mOS (19.8 vs. 11.4, HR 0.53) as compared to those with TMB ≥10 and <16 Muts/Mb[336]. In a retrospective analysis of patients with 17 solid tumor types (comprised of 47% NSCLC, 40% urothelial carcinoma, and 13% encompassing 15 other solid tumors), TMB of 16 Muts/Mb or greater was reported to be associated with an improved ORR to atezolizumab compared to chemotherapy (30% vs. 14%)[12]. Atezolizumab has been studied primarily for the treatment of non-small cell lung cancer (NSCLC)[337-342] and urothelial carcinoma[343-346] . A study of atezolizumab as monotherapy for patients with advanced solid tumors reported a median PFS of 18 weeks and an ORR of 21%, including confirmed responses in 25.6% (11/43) of melanomas, 12.5% (7/56) of renal cell carcinomas (RCC) and 16.7% (1/6) of colorectal cancers (CRCs)[342]. As single-agent therapy in genomically unselected young patients (<30 years old) with relapsed or refractory cancers, atezolizumab elicited an ORR of 1.5% (1/67) for patients with solid tumors, with similar safety and pharmacokinetics as seen in adults[347]. A Phase 1a study of atezolizumab reported an ORR of 14.5% (9/62), a median PFS of 5.6 months, and a median OS of 28.9 months for patients with clear cell RCC[348]. A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 41.7% (10/24) of patients; no dose-limiting toxicities were observed[349]. A Phase 1b study that evaluated atezolizumab in combination with the MEK inhibitor cobimetinib for advanced solid tumors reported an ORR of 8.3% (7/84) in patients with CRC, 40.9% (9/22) in patients with melanoma, 17.9% (5/28) in patients with NSCLC, and 18.8% (3/16) in patients with other tumors (ovarian cancer, clear-cell sarcoma, and RCC); there was no association between BRAF or KRAS mutation status and response rate in any disease setting, and no dose-limiting toxicities were encountered[350-351] .

Avelumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

The 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)[352], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[353], urothelial carcinoma[354], mesothelioma[355], ovarian carcinoma[356], and breast cancer[357], and from avelumab combined with axitinib in renal cell carcinoma[358]. 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[352,356-357] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[359-361] .

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Cabozantinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[362-363] , as well as by extensive preclinical data[364-370] .

SUPPORTING DATA

A randomized Phase 2 discontinuation study of cabozantinib in 9 solid tumor types reported ORRs of 0% to 22% and response durations of 3.3 to 11.2 months across cohorts with ORRs of 10% or greater observed for patients with ovarian cancer (22% [15/69, 1 CR]), metastatic breast cancer (14% [6/44]), and non-small cell lung cancer (NSCLC) (10% [6/60])[371-372] . A Phase 1 study of cabozantinib for advanced solid tumors reported a 17% (4/23) ORR in the dose escalation cohort and an ORR of 20% (4/20) and a DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[373]. In the context of studies for specific solid tumors, the randomized Phase 3 EXAM study for patients with advanced medullary thyroid cancer reported an association of cabozantinib with improved PFS compared with placebo (11.2 vs. 4.0 months, HR=0.28) and a higher ORR (28% vs. 0%), with PFS improvement observed regardless of RET mutation status[374]. The randomized Phase 3 CELESTIAL study for patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib reported significantly longer OS (10.2 vs. 8.0 months, HR=0.76) and PFS (5.2 vs. 1.9 months, HR=0.44) as well as an increased ORR (3.8% vs. 0.4%) with cabozantinib when compared to placebo[375]. The Phase 2 CABOSUN trial of first line cabozantinib versus sunitinib for patients with intermediate- or poor-risk advanced clear cell renal cell carcinoma demonstrated significantly improved median PFS (8.2 vs. 5.6 months, HR=0.66), prolonged median OS (30.3 vs. 21.8 months), and higher ORR (33% [26/79] vs. 12% [9/78]) with cabozantinib compared with sunitinib[376]. The Phase 2 CABONE study of cabozantinib reported ORRs of 26% (10/39) for patients with advanced Ewing sarcoma and 12% (5/42) for patients with advanced osteosarcoma[377].

Capmatinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[105,111-114,378] , hepatocellular carcinoma[110], renal cell carcinoma[115], and gastric cancer[116], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[106,379-380] or MET exon 14 skipping alterations[380-381] as well as in combination with EGFR inhibitors for patients with MET amplification[107-109] . Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with MET-amplified glioblastoma (n=10)[382], MET-overexpressing gastric cancer (n=9)[383], or other advanced solid tumors with MET amplification or overexpression (n=11)[383-384] .

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Cemiplimab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[385]. A Phase 2 trial of cemiplimab in patients with basal cell carcinoma (BCC) reported ORRs of 31% (5 CRs and 21 PRs) in patients with locally advanced BCC and 21% (6 PRs) in patients with metastatic BCC[386-387] . The Phase 3 EMPOWER-Lung 1 trial for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50% reported that cemiplimab is associated with improved PFS (8.2 vs. 5.7 months), OS (not reached vs. 14.2 months), and ORR (37% vs. 21%) compared with chemotherapy[388].

Crizotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), and to treat pediatric and young adult patients with ALK rearrangement-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[98-100,389-390] , gastric cancer[160], gastroesophageal cancer[102], glioblastoma[103], and carcinoma of unknown primary[104], as well as in patients with MET-mutated cancers, including NSCLC[362,391-395] , renal cell carcinoma (RCC)[396], and histiocytic sarcoma[391]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[362,391,393-395,397] .

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[398-402] , ROS1 rearrangements[403-407] , an NTRK1 fusion[408], or MET activation[98-100,362,389-390,392-395,409-415] . Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[416] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[102-104] . While a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) in patients with lymphoma and inflammatory myofibroblastic tumors (IMT), respectively, an ORR of 11.8% (2/17) was reported for patients with other types of tumors[417]. Whereas median PFS and median OS were not reached for patients with lymphoma or IMT, median PFS was 1.3 months and median OS was 8.3 months for patients with other tumor types, and the median duration of treatment was ~1 month relative to 1-3 years for patients with lymphoma or IMT[417]. A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 14/79 patients, including nine CRs and five PRs; response was enriched in patients with activating alterations in ALK[418].

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Durvalumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Single-agent durvalumab has demonstrated efficacy in non-small cell lung cancer[419-420] , and head and neck squamous cell carcinoma[421-422] . 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[423-424] . 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[425]. 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[426] and in patients with BRCA-wild-type breast or gynecological cancer[427]. 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[428]. Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680[429], the CXCR2 antagonist AZD5069[430], or the ATR inhibitor AZD6738[431]. 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[432].

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Nivolumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,12,309] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

Nivolumab monotherapy has been reported to elicit clinical benefit for patients with multiple types of solid tumors, including melanoma (27-31% ORR)[433-437] , non-small cell lung cancer (NSCLC; 17-20% ORR and 9-10 months median OS [mOS] for unselected patients)[438-444] , urothelial carcinoma (20-26% ORR for unselected patients)[445-446] , renal cell carcinoma (RCC; 26% ORR)[447-452] , microsatellite instability-high (MSI-High) colorectal cancer (CRC; 58% ORR)[453-455] , head and neck squamous cell carcinoma (11-17% ORR)[456-458] , ovarian cancer (6-15% ORR)[459-461] , small cell lung cancer (SCLC; 10-12% ORR)[355,462-463] , gastroesophageal carcinoma (12-18% ORR)[464-466] , and cancer of unknown primary (CUP; 22% ORR for unselected, previously treated patients)[467], as well as with Hodgkin lymphoma (66-87% ORR)[468-470] . Combination treatment with nivolumab plus the CTLA-4 inhibitor ipilimumab has achieved further efficacy in melanoma (up to 61% ORR; mOS >60 months for the combination vs. 37 months for nivolumab monotherapy)[433,471-473] , NSCLC (mOS of 17 months)[474], MSI-High CRC (64% ORR)[475], RCC (42% ORR)[476-477] , SCLC (19-25% ORR)[355,463] , urothelial carcinoma (38% ORR for unselected patients; 58% ORR for patients with ≥1% tumor PD-L1 expression)[445], and other solid tumors. Combinations of nivolumab with various targeted therapies, such as pazopanib (1 PR for a patient with epithelioid sarcoma)[478], sunitinib (9% ORR for unselected patients with sarcoma)[479], cabozantinib (29% ORR for patients with immunotherapy-refractory urothelial carcinoma)[480], or vemurafenib (1 durable PR for a patient with BRAF-V600E-mutated and PD-L1-positive anaplastic thyroid cancer)[481], have also shown evidence of efficacy and continue to undergo clinical investigation.

Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
63 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,482] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

Combination treatment with nivolumab plus the CTLA-4 inhibitor ipilimumab has achieved efficacy in melanoma (up to 61% ORR; mOS >60 months for the combination vs. 37 months for nivolumab monotherapy)[433,471-473] , NSCLC (17 months mOS)[474], MSI-High CRC (64% ORR)[475], RCC (42% ORR)[476-477] , SCLC (19–25% ORR)[355,463] , urothelial carcinoma (38% ORR in unselected patients; 58% ORR in patients with ≥1% tumor PD-L1 expression)[445], and other solid tumors.

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Tepotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[105,111-114,378] , hepatocellular carcinoma[110], renal cell carcinoma[115], and gastric cancer[116], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[111] and MET exon 14-skipping alterations[483-484] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[113-114] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[110,485-487] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[488]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[489].

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

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

BIOMARKER

Tumor Mutational Burden

RESULT

63 Muts/Mb

RATIONALE

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

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT04589845

PHASE 2

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

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

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

NCT04521621

PHASE 1/2

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

TARGETS
PD-1

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

NCT04261439

PHASE 1

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

TARGETS
PD-1

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

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NCT03799003

PHASE 1

A Study of ASP1951 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, TNFRSF18

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Daegu (Korea, Republic of), Chungcheongbukdo (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Washington, California, Utah

NCT03861793

PHASE 1/2

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

TARGETS
PD-1

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

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

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

NCT03396445

PHASE 1

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

TARGETS
PD-1, CD27

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

NCT04892498

PHASE 2

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

TARGETS
PD-1

LOCATIONS: Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

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GENE
ERBB3

ALTERATION
V104L

RATIONALE
Clinical and preclinical data support sensitivity of ERBB3 activating mutations to HER2-targeting TKIs, including afatinib and lapatinib. ERBB3 amplification or activating mutations may confer sensitivity to therapies targeting ERBB3.

NCT03810872

PHASE 2

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

TARGETS
EGFR, ERBB4, ERBB2

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

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GENE
MET

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

ALTERATION
amplification

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), North Adelaide (Australia), Bedford Park (Australia)

NCT04647838

PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

NCT04887194

PHASE 1

PK Study to Assess Drug-drug Interaction and QTc Between Sitravatinib and a Cocktail of Substrates

TARGETS
AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB, PD-1

LOCATIONS: Texas, Virginia

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NCT04693468

PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

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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. Please note that some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

ABL1
S1007*

ALK
E201Q

ARID2
H48Y

ASXL1
I980N

BCORL1
D77N and T1111M

BRCA1
G1232L

BRD4
E657Q

BRIP1
R814C

CD22
S105N

CIC
A531T

CIITA
A462S and A648E

EPHA5
E881D and T176A

EPHB1
I236M

ERBB4
A345V, D1131Y and P1132H

FAM123B
G327C

FBXO11
S34N

FBXO31
R19P

FLT4
A634D and Y435C

FRS2
P240S

GPR124
R369Q

HGF
G31*

HIST1H1C
E3K

HIST1H3B
A92P

IL7R
K104N and L123V

JUN
R221Q

LRP1B
S1198Y and S913R

MAPK1
D210H

MKI67
I2578V

MYST3
A1442S and P1766L

NOTCH1
P1884Q

NSD1
R1074L

NTRK2
A187E

P2RY8
P341H

PCLO
E3034D and P995A

PDGFRA
A7P

PLCG2
E1208K

POT1
T425A

PPP2R1A
V259F

PRKDC
D3411H

SMARCA4
D1183Y

SMC3
E998*

SMO
R703P

SOCS1
L150Q

SOX2
A30S

SPEN
S2185F

SUZ12
S53L

TAF1
R123T

TNFAIP3
E451Q

TSHR
G235R

WDR90
R690Q

ZNF217
P823L

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FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*		*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*	*B2M*
BAP1	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*	*BCOR*
BCORL1	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BRSK1*
BTG2	*BTK*	*BTLA*	*C11orf30 (EMSY)*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274 (PD-L1)*	*CD36*	*CD58*
CD70	*CD79A*	*CD79B*	*CDC73*	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*
CDKN1B	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*
CIITA	*CKS1B*	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*	*DNMT3A*
DOT1L	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*	*EGFR*	*ELP2*
EP300	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*	*ERG*
ESR1	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*	*FAF1*	*FAM46C*	*FANCA*	*FANCC*
FANCD2	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*	*FBXW7*
FGF10	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*
FGFR3	*FGFR4*	*FHIT*	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*
FOXO1	*FOXO3*	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4 (C17orf39)*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*	*HIST1H2AC*	*HIST1H2AG*
HIST1H2AL	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*	*HIST1H3B*	*HNF1A*	*HRAS*
HSP90AA1	*ICK*	*ID3*	*IDH1*	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*	*IKZF2*
IKZF3	*IL7R*	*INHBA*	*INPP4B*	*INPP5D (SHIP)*	*IRF1*	*IRF4*	*IRF8*	*IRS2*
JAK1	*JAK2*	*JAK3*	*JARID2*	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*
KRAS	*LEF1*	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*	*MDM2*
MDM4	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*	*MITF*	*MKI67*
MLH1	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*
MYCL (MYCL1)	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*
NFKBIA	*NKX2-1*	*NOD1*	*NOTCH1*	*NOTCH2*	*NPM1*	*NRAS*	*NT5C2*	*NTRK1*
NTRK2	*NTRK3*	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*
PAX5	*PBRM1*	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*
PTPN2	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*	*RARA*	*RASGEF1A*
RB1	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*RUNX1*
S1PR2	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SERP2*	*SETBP1*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA1*	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*
SOCS1	*SOCS2*	*SOCS3*	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*
STAG2	*STAT3*	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*
TAF1	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	
TMSB4XP8 (TMSL3)		*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*
U2AF2	*VHL*	*WDR90*	*WHSC1 (MMSET or NSD2)*		*WISP3*	*WT1*	*XBP1*	*XPO1*
YY1AP1	*ZMYM3*	*ZNF217*	*ZNF24 (ZSCAN3)*	*ZNF703*	*ZRSR2*			

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*Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS*

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26 (GRAF)*	
ARHGEF12	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*	*BCL10*	*BCL11A*
BCL11B	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*	*BCR*	*BIRC3*
BRAF	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CHIC2*	*CHN1*	*CIC*	*CIITA*	*CLP1*
CLTC	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*
CTNNB1	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*	*EGFR*	*EIF4A2*	*ELF4*
ELL	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*
FGFR1OP	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*	*FOXO4*	*FOXP1*
FSTL3	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*	*HEY1*	*HIP1*
HIST1H4I	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*	*HOXA9*	*HOXC11*
HOXC13	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*	*IGL*	*IKZF1*
IL21R	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*	*JAZF1*	*KAT6A (MYST3)*
KDSR	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*	*LPP*	*LYL1*
MAF	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1 (ENL)*	*MLLT10 (AF10)*
MLLT3	*MLLT4 (AF6)*	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*
MYC	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*	*NF2*
NFKB2	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*
NUMA1	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*	*PAFAH1B2*	*PAX3*	*PAX5*
PAX7	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*	*PDE4DIP*	*PDGFB*	*PDGFRA*	*PDGFRB*
PER1	*PHF1*	*PICALM*	*PIM1*	*PLAG1*	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*
PRDM16	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*	*RABEP1*	*RAF1*	*RALGDS*	*RAP1GDS1*
RARA	*RBM15*	*RET*	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*
RUNX1T1 (ETO)	*RUNX2*	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*
SNX29 (RUNDC2A)	*SRSF3*	*SS18*	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*STL*	*SYK*
TAF15	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*
TFG	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*
TPM3	*TPM4*	*TRIM24*	*TRIP11*	*TTL*	*TYK2*	*USP6*	*WHSC1 (MMSET or NSD2)*	
WHSC1L1	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*			

*Note: some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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Electronically signed by Leah Commander, M.D. | 19 April 2022
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

The median exon coverage for this sample is 761x

ACCURACY		
Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8 copies	>95.0%
Sensitivity: Microsatellite Instability-High (MSI-H) status	Positive Predictive Agreement (PPA)	100.0% (87.54%-100.00%)*
Sensitivity: Microsatellite Stable (MSS) status	Positive Predictive Agreement (PPA)	89.66% (81.50%, 94.46%)*
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite Instability-High (MSI-H) status	Negative Predictive Agreement (NPA)	97.44% (91.12%-99.29%)*
Specificity: Microsatellite Stable (MSS) status	Negative Predictive Agreement (NPA)	94.44% (86.57%, 97.82%)*
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

*95% Confidence Interval

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne®Heme, please refer to the article He, J. et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting, Blood (2016 Jun. 16).

In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the FoundationOne Heme 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 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.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne Heme test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne Heme samples and is reported as the number of mutations per megabase (Muts/Mb). Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

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ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across 265 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

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. 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 Heme 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 FoundationOne Heme 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 Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme 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.

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 Heme.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme 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.

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CE

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.

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, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, 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.

SELECT ABBREVIATIONS

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

MR Suite Version 6.1.0

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