ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Lung adenocarcinoma

DATE OF BIRTH 17 November 1954
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID OG 11/17/1954
SPECIMEN TYPE Blood
DATE OF COLLECTION 17 November 2021
SPECIMEN RECEIVED 22 November 2021

Biomarker Findings

Blood Tumor Mutational Burden - 25 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 21%

Genomic Findings

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

AKT2 amplification
STK11 Q220*
CCNE1 amplification - equivocal†
CIC E1356*
MUTYH Q216*
RB1 R355fs*6
TP53 M246L

† See About the Test in appendix for details.

7 Therapies with Clinical Benefit
0 Therapies with Resistance
24 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 25 Muts/Mb	Atezolizumab 1 Cemiplimab 1 Durvalumab 1 Nivolumab 1 Pembrolizumab 1 Dostarlimab	Avelumab
10 Trials see p. 17		
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).	
Tumor Fraction - 21%	Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.	

GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
AKT2 - amplification	-	None	None
10 Trials see p. 19			

☐ *NCCN category*

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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
STK11 **-** Q220*	13.4%	None	None
8 Trials see p. 21			

☐ *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >30%. See appendix for details.

MUTYH **-** Q216* p. 9

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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.

CCNE1 - amplification - equivocal p. 8
CIC - E1356* p. 8
MUTYH - Q216* p. 9
RB1 - R355fs*6 p. 9
TP53 - M246L p. 10

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies 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/or exhaustive. Neither the therapies 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 or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

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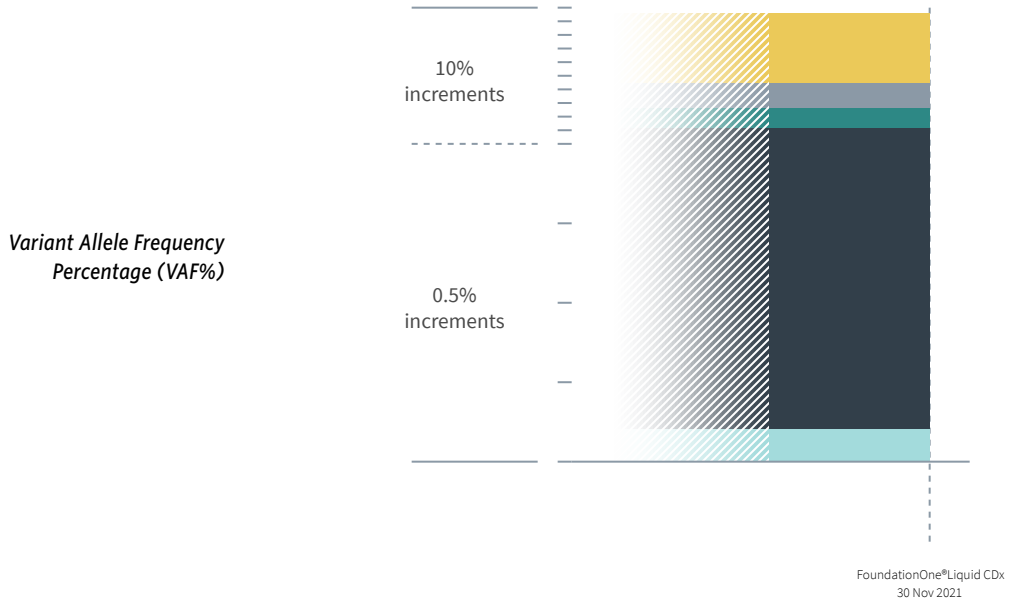

HISTORIC PATIENT FINDINGS		ORD-1245373-01 VAF%
Blood Tumor Mutational Burden		25 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		21%
AKT2	amplification	Detected
STK11	● Q220*	13.4%
CCNE1	amplification	Detected
CIC	● E1356*	14.7%
MUTYH	● Q216*	51.2%
RB1	● R355fs*6	0.21%
TP53	● M246L	18.4%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

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Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene
Not Detected = baited but not detected on test
Detected = present (VAF% is not applicable)
VAF% = variant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
25 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB <7 Muts/Mb for patients treated with docetaxel[5]. In one study of advanced NSCLC in China, bTMB ≥6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB <6 Muts/Mb for patients treated with platinum-based chemotherapy[6]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[7]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[8]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[8-9].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

BIOMARKER

Tumor Fraction

RESULT
21%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[21]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[22-27].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[28]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[29], Ewing sarcoma and osteosarcoma[30], prostate cancer[25], breast cancer[31], leiomyosarcoma[32], esophageal cancer[33], colorectal cancer[34], and gastrointestinal cancer[35].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[36], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[37-38].

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GENE
AKT2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or activation of AKT2 may promote AKT-mTOR pathway activation and may predict sensitivity to inhibitors of the AKT and downstream mTOR pathways. Clinical benefit has been achieved in 1 patient with AKT2 amplification treated with an mTOR inhibitor[39]. In preclinical studies, the AKT inhibitor MK-2206 showed evidence of enhancing anti-tumor activity of other chemotherapeutic agents in lung and ovarian tumor cells[40].

FREQUENCY & PROGNOSIS

Alterations in the PI3K-AKT signaling pathway are frequent in lung cancer[41]. In the TCGA datasets, AKT2 amplification has been reported in 1.3% of lung adenocarcinoma cases[42] and 4.5% of lung squamous cell carcinoma (SCC) cases[43]. AKT2 mutation has been reported in 2.6% of lung carcinoma samples analyzed in COSMIC (Dec 2020)[44]. Increased expression of AKT2 protein has been reported in patients with non-small cell lung cancer (NSCLC) and has been correlated with reduced progression-free and overall survival, as well as lymph node metastasis[45]. Phosphorylation of AKT2 may be a stronger predictor of outcome in patients with NSCLC than AKT2 amplification or AKT2 mRNA expression[46-48].

FINDING SUMMARY

AKT2 encodes an intracellular serine/threonine kinase that is also known as PKB-beta. AKT2 is one of three members of the AKT gene family, and activation of AKT2 has been implicated in multiple malignancies[49-50]. AKT isoforms appear to have different roles in tumorigenesis; AKT1 appears to contribute to the initiation of tumors, whereas AKT2 promotes invasion and metastasis in breast tumors[51]. Although AKT2 amplification has been reported to associate with AKT2 overexpression[52-54], studies in various cancers suggest that AKT2 phosphorylation may have greater clinical relevance than AKT2 amplification or mRNA overexpression[41,46].

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GENE
STK11

ALTERATION
Q220*

TRANSCRIPT ID
NM_000455

CODING SEQUENCE EFFECT
658C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[55-59]. Case studies have reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus[60], with 1 PR observed in a PJS patient for 9 months until progression[60]. However, retrospective analysis of a Phase 2 trial for patients with endometrial carcinoma found LKB1 (STK11) protein levels were not significantly correlated with response to everolimus treatment[61]. In one preclinical study, STK11 loss was associated with sensitivity to combination treatment including an SRC inhibitor[62]; however, the clinical relevance of these findings has not been established.

— Potential Resistance —

STK11 alteration is associated with poorer response to immune checkpoint inhibitors for patients with non-small cell lung cancer (NSCLC), including those with tumors harboring co-occurring KRAS or KEAP1 mutations. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS and STK11 co-mutated tumors than for patients with wild-type STK11 (6.4 vs. 16.1 months, HR=1.99)[63], as well as markedly fewer objective responses for patients with KRAS/STK11 co-mutated versus KRAS/TP53 co-mutated tumors in the CheckMate-057, CheckMate-012, and GEMINI trials (0% vs. 53-78%%)[63-64], although a case study reported ongoing response for 1 patient with KRAS/STK11 co-mutations treated with nivolumab and ipilimumab[65]. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor 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-wild-type tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[66]. However, exploratory analyses of patients with NSCLC treated in the first-line setting with pembrolizumab showed trends towards improved ORR and OS irrespective of STK11 or KEAP1 mutation status, though this was not demonstrated to be statistically significant[67-68] . In the absence of co-mutations, reduced clinical benefit has also been reported for patients with NSCLC harboring STK11 mutations compared with wild-type STK11 and either anti-PD-L1[69-70] or anti-PD-1 therapy[71].

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)[43,56,72-76]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases[42] and was not observed in any of 178 lung squamous cell carcinoma cases[43]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations[74-75]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas[56]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab[77].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels[55]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[62,78]. Alterations such as seen here may disrupt STK11 function or expression[79-90].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the STK11 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Peutz-Jeghers syndrome (ClinVar, Sep 2021)[91]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[92]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[92-94]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[92-94], and individuals with this syndrome have a 30-50% risk of developing breast cancer[92,94]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

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GENE
CCNE1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1 pathway[95] and cyclin E1 promotes cell cycle progression in a complex with CDK2[96], clinical and preclinical studies have investigated inhibitors of CHK1, ATR, and CDK2 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade ovarian carcinoma with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[97]. Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[98-99] or CDK2[100]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[101-104]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[105].

FREQUENCY & PROGNOSIS

In the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets, putative high-level CCNE1 amplification has been reported in 2.6%[42] and 5.6%[43] of cases, respectively. CCNE1 amplification was identified in 6% (6/98) of patients with non-small cell lung cancer (NSCLC) and was associated with TP53 mutation[106]. A study of 68 NSCLC samples observed cyclin E1 overexpression to significantly correlate with centrosome abnormalities[107]. Published data investigating the prognostic implications of CCNE1 in NSCLC are limited (PubMed, Jul 2021).

FINDING SUMMARY

CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[96]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[108-109]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[110-111]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[96,112].

GENE
CIC

ALTERATION
E1356*

TRANSCRIPT ID
NM_015125

CODING SEQUENCE EFFECT
4066G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CIC.

FREQUENCY & PROGNOSIS

CIC mutations have been described in various solid tumors, including 1–10% of sequenced gastric, endometrial, and colorectal carcinomas and melanoma tumors (cBioPortal, COSMIC, Jan 2021)[44,113-114], although the consequences of CIC mutations in these tumor types have not been studied. CIC mutations have been observed in 58–69% of oligodendrogliomas but are less common in other gliomas, such as astrocytoma or oligoastrocytoma[115-117]. Published data investigating the prognostic implications of CIC alterations are generally limited (PubMed, Jun 2021). Conflicting data have been reported regarding the prognostic significance of CIC mutation in oligodendroglioma[116,118-119].

FINDING SUMMARY

CIC encodes a transcriptional repressor that plays a role in central nervous system (CNS) development[120]. CIC inactivation has been reported in various malignancies, and is highly recurrent in oligodendroglioma[115-116].

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GENE
MUTYH

ALTERATION
Q216*

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
646C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2021)[44]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[121-122]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[123-125]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[126].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[127]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[121-122,128-130]. Numerous other MUTYH mutations have also been shown to result in loss of function[128-131].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with MUTYH-associated polyposis (ClinVar, Sep 2021)[91]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[121,132-134]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[121]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[135-139]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[122]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
RB1

ALTERATION
R355fs*6

TRANSCRIPT ID
NM_000321

CODING SEQUENCE EFFECT
1064_1065delGA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[140] and strong preclinical data[141-143], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit[144]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[145] and activation of the NOTCH pathway[146].

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb[147-156].

— Nontargeted Approaches —

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer[157-158].

FREQUENCY & PROGNOSIS

In the TCGA dataset, RB1 mutation was observed in 5% of lung squamous cell carcinoma cases[43] and 4% of lung adenocarcinoma cases[42]. Loss of Rb protein expression has been reported in 62% of pre-chemotherapy advanced non-small cell lung cancers (NSCLC)[159]. One study found that RB1 expression was correlated with poor prognosis for patients with NSCLC[160].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[158,161]. Alterations such as seen here may disrupt RB1 function or expression[162-168].

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[169]. Germline mutations in RB1 account for approximately 40% of RB tumors[170] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[171-172]. In the appropriate clinical context, germline testing of RB1 is recommended.

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GENE
TP53

ALTERATION
M246L

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
736A>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[173-176], or p53 gene therapy and immunotherapeutics such as SGT-53[177-181] and ALT-801[182]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[183]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[184]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[185]. 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[186]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[187]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[188]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[181]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[189]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[190-192]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[193]. 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[194-195]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[196-197]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[42-43,198-203], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[42-43,76,204]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[113-114]. 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[205]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[206].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[207]. Alterations such as seen here may disrupt TP53 function or expression[208-212].

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[213-215], including sarcomas[216-217]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[218] to 1:20,000[217]. 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[219]. 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[220-225]. 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[220-221]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[226]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[224,227-228]. 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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Atezolizumab

Assay findings association

Blood Tumor Mutational Burden
25 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[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 2 B-F1RST study prospectively evaluated blood tumor mutational burden (bTMB) as a biomarker of response to first-line atezolizumab in non-small cell lung cancer (NSCLC), reporting improved ORR (29% vs. 4.4%) and a trend toward improved median PFS (mPFS; 5.0 vs. 3.5 months, HR=0.80) and median OS (mOS; 23.9 vs. 13.4 months, HR=0.66) for patients with bTMB ≥16 Muts/Mb compared with bTMB <16 Muts/Mb; improved PFS and OS were seen with increasing bTMB cutoffs[230]. Retrospective analysis of the Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic NSCLC reported improved mOS (11.2 vs. 10.3 months, HR=0.87) and mPFS (5.5 vs. 4.3 months, HR=0.74) compared with chemotherapy for patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay), with greater efficacy observed at higher bTMB cutoffs[231]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic NSCLC reported atezolizumab significantly improved OS across bTMB levels compared with docetaxel (p=0.0001); patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay) achieved greater clinical benefit with atezolizumab than those with bTMB <10 Muts/Mb, with greater efficacy observed at higher bTMB cutoffs[1,232] ; patients with two or more mutations in DNA damage response and repair pathway genes (DDR) had an increased bTMB (20 vs. 7 muts/Mb), and reported a superior durable clinical benefit compared with patients without DDR mutations (57% vs. 31%, p=0.003)[233]. In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[234-236] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[235]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[234]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[236]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[231]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[237], confirming previous Phase 2 trial data[238-239] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[237]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[240], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[233]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[241]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[242].

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Cemiplimab

Assay findings association

Blood Tumor Mutational Burden
25 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[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[243]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[244].

Dostarlimab

Assay findings association

Blood Tumor Mutational Burden
25 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[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[245]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[246-248] . 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[246,249] .

Durvalumab

Assay findings association

Blood Tumor Mutational Burden
25 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[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The MYSTIC trial for patients with treatment-naïve, EGFR/ALK-negative metastatic NSCLC reported that a bTMB score ≥20 Muts/Mb (approximately 10 Muts/Mb as measured by this assay) associated with improved survival following either a combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab, regardless of tumor PD-L1 expression, or following durvalumab monotherapy for patients with tumor cell PD-L1 expression <1%[229]. In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[250-251] . In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[252]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[252]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 vs. HR=0.85); however, patients with blood tumor mutational burden (bTMB) ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[253]. In the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC, the addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs 4.8 months, HR=0.72) versus chemotherapy[254]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[255-256] and OS[255] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity[256]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[257].

Nivolumab

Assay findings association

Blood Tumor Mutational Burden
25 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[258]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[259-260] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[261]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[262], despite Phase 1 results in the same setting suggesting improved ORR and OS[263]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[264]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[265].

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Pembrolizumab

Assay findings association

Blood Tumor Mutational Burden
25 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 gastric, esophageal, or gastroesophageal junction (GEJ) cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or GEJ cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information. A voluntary withdrawal of the accelerated approval of pembrolizumab for the treatment of patients with recurrent advanced PD-L1-positive gastric or GEJ adenocarcinoma with disease progression on or after two or more prior lines of therapy has been initiated by the manufacturer.

GENE ASSOCIATION

On the basis of clinical data[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

A pilot study for first-line pembrolizumab alone or in combination with chemotherapy, for patients with newly diagnosed metastatic NSCLC, reported significantly improved median PFS in patients with bTMB levels ≥16 Muts/Mb (approximately 8 Muts/Mb as measured by this assay) compared with those with bTMB <16 Muts/Mb (14.1 vs. 4.7 months, HR=0.30); median OS was not reached in the bTMB ≥16 Muts/Mb cohort, compared with 8.8 months for those with bTMB <16 (HR=0.48)[3]. The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[266] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[267], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[267]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[268]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[269]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[270] or squamous (KEYNOTE-407)[271-272] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[273]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[274]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[275]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[276]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[277-279] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[280], the anti-CTLA-4 antibody ipilimumab[281], the anti-TIGIT antibody vibostolimab[282], the HDAC inhibitor vorinostat[283], the multikinase inhibitor lenvatinib[284], and the PARP inhibitor niraparib[285].

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Avelumab

Assay findings association

Blood Tumor Mutational Burden
25 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[1-3,229] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[286], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[287]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[288]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[289]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[290]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[291]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[292].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

Electronically signed by Naomi Lynn Ferguson, M.D. | 30 November 2021
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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

25 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.

NCT03800134

PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), San José (Costa Rica), Temuco (Chile), Buenos Aires (Argentina), Guatemala (Guatemala)

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: San Isidro (Peru), Lima (Peru), Arequipa (Peru), Ijui (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Cdmx (Mexico), Mexico (Mexico), Querétaro (Mexico), Florida

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Ciudad Autonoma De Buenos Aire (Argentina), Texas, Alabama, Georgia, South Carolina, North Carolina, Tennessee, Kentucky

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ORDERED TEST # ORD-1245373-01

CLINICAL TRIALS

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida

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: Lima (Peru), Taichung (Taiwan), New Jersey, Toronto (Canada), Montreal (Canada), Oregon, Madrid (Spain), Barcelona (Spain), Villejuif (France), Marseille (France)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

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

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Florida, Hsinchu (Taiwan), Missouri, Illinois, Kharkiv (Ukraine), Kryvyi Rih (Ukraine)

NCT03425643

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage IIB or IIIA Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)

TARGETS
PD-1

LOCATIONS: San Juan (Argentina), Cordoba (Argentina), Rosario (Argentina), Ijui (Brazil), Berazategui (Argentina), Brasilia (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Florianopolis (Brazil), Sao Paulo (Brazil)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

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

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico), San Juan (Puerto Rico), Ipatinga (Brazil)

GENE
AKT2

ALTERATION
amplification

RATIONALE
AKT2 amplification or mutation may lead to AKT-mTOR pathway activation and may predict sensitivity to inhibitors of this pathway.

NCT01737502

PHASE 1/2

Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer

TARGETS
mTOR

LOCATIONS: Florida

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Texas, Tennessee, Virginia, District of Columbia, Maryland, Missouri, Pennsylvania, New York, Massachusetts

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

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

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

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CLINICAL TRIALS

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

GENE
STK11

ALTERATION
Q220*

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Texas, Tennessee, Virginia, District of Columbia, Maryland, Missouri, Pennsylvania, New York, Massachusetts

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT04250545

PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS
mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ALK
Y276C

ARID1A
M332V

BRD4
A1189T

CD22
amplification

CHEK2
S192L

CTNNB1
R717H

EGFR
D537fs*6

EPHA3
E772V and T351K

FAM123B
A187S

FGF10
amplification

HGF
E670D

IGF1R
E1326L and M826L

MAP2K4
D101N

MLL2
G1811S and P2210A

MSH2
G683V

MST1R
R396Q

NF1
A2553P

NFE2L2
H398P

PARP1
K816R

PAX5
R305C

PBRM1
R643S

RICTOR
amplification

SDHA
amplification

SMO
R173L

SPEN
S3635F

TEK
A539S

TSC1
K587R

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ORDERED TEST # ORD-1245373-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

Electronically signed by Naomi Lynn Ferguson, M.D. | 30 November 2021
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FoundationOne Liquid 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. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.
11. Alterations reported may include somatic (not

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inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.

12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

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 >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, 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.

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. 2021. 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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.1.1

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Electronically signed by Naomi Lynn Ferguson, M.D. | 30 November 2021
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