FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung cancer (NOS)
COUNTRY CODE
PE

REPORT DATE
29 Mar 2021
ORDERED TEST #
ORD-1046086-01

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 cancer (NOS)

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

PHYSICIAN

MEDICAL FACILITY Oncologia Patologica
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 320946
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID PAU 7/17/1954
SPECIMEN TYPE Blood
DATE OF COLLECTION 11 March 2021
SPECIMEN RECEIVED 18 March 2021

Biomarker Findings

Blood Tumor Mutational Burden - 18 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 19%

Genomic Findings

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

FBXW7 Q41*
STK11 L85*
BRAF K601N
KRAS G12R
APC rearrangement exon 16
ATRX S1125fs*28, inversion exons 3-9, L767fs*1
CDKN2A/B p16INK4a Y44fs*1
CREBBP R1446C
DNMT3A R882H, Y481*, P904L, splice site 1015-1G>T, R635Q
KEL splice site 1593-1G>T
NKX2-1 amplification - equivocal†
SMARCA4 splice site 2973+1G>C
TP53 S241C, P152L, G245V, G154V

† See About the Test in appendix for details.

8 Therapies with Clinical Benefit
0 Therapies with Lack of Response
35 Clinical Trials

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - 18 Muts/Mb

10 Trials see p. 21

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Atezolizumab	1	Avelumab
Cemiplimab	1	
Durvalumab	1	
Nivolumab	1	
Pembrolizumab	1	

Microsatellite status - MSI-High Not Detected

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

Tumor Fraction - 19%

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 BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
FBXW7 -	Q41*	1.8%	None	Everolimus
				Temsirolimus

10 Trials see p. 25

☐ *NCCN category*

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GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
STK11 -	L85*	14%	None	Everolimus Temsirolimus
10 Trials see p. 29				
BRAF -	K601N	12.3%	None	None
10 Trials see p. 23				
KRAS -	G12R	3.7%	None	None
10 Trials see p. 27				

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the 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*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *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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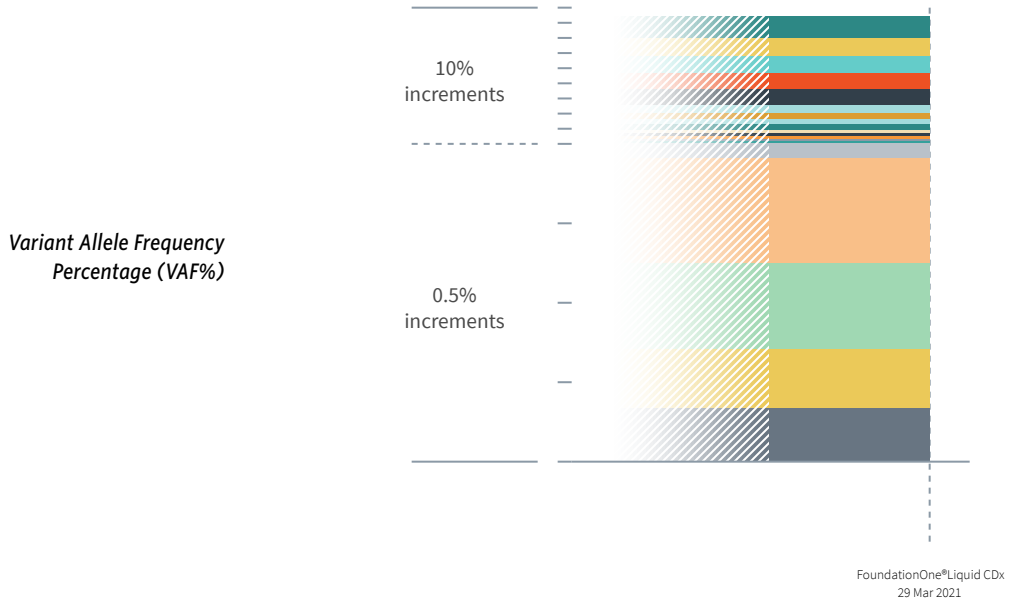

HISTORIC PATIENT FINDINGS		ORD-1046086-01 VAF%
Blood Tumor Mutational Burden		18 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		19%
FBXW7	Q41*	1.8%
STK11	L85*	14%
BRAF	K601N	12.3%
KRAS	G12R	3.7%
APC	rearrangement exon 16	0.27%
ATRX	L767fs*1	1.4%
	S1125fs*28	1.5%
	inversion exons 3-9	2.3%
CDKN2A/B	p16INK4a Y44fs*1	2.6%
CREBBP	R1446C	3.7%

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HISTORIC PATIENT FINDINGS		ORD-1046086-01 VAF%
DNMT3A	R635Q	1.4%
	R882H	1.1%
	splice site 1015-1G>T	0.54%
	P904L	0.34%
	Y481*	11.1%
KEL	splice site 1593-1G>T	10.8%
NKX2-1	amplification	Detected
SMARCA4	splice site 2973+1G>C	0.66%
TP53	G154V	10.1%
	S241C	3.6%
	P152L	0.37%
	G245V	5.6%

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%.

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
18 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

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]. Published data investigating the prognostic implications of bTMB levels in lung cancer are limited (PubMed, Jul 2020). 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)[5]. 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[6]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[6-7].

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[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. 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
19%

POTENTIAL TREATMENT STRATEGIES

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. 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[19-24].

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)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

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[33], 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[34-35].

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GENE
FBXW7

ALTERATION
Q41*

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
121C>T

POTENTIAL TREATMENT STRATEGIES
Based on clinical evidence from studies of several patients with lung, renal, liver, and other cancers[36-38] and extensive preclinical evidence[39-42], FBXW7 loss or inactivation may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Reduction in FBXW7 was reported to result in accumulation of the FBXW7 substrates NOTCH1, c-MYC, and cyclin E[43], but therapeutic strategies targeting these proteins have not been tested in the context of FBXW7 inactivation[44-52]. FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[53].

FREQUENCY & PROGNOSIS
In the TCGA datasets, FBXW7 mutation was observed in 3% of lung squamous cell carcinoma (SCC) cases[54] and in 1.7% of lung adenocarcinoma cases[55]. Decreased FBXW7 expression has been reported in non-small cell lung cancer (NSCLC) and associated with disease progression and shorter patient survival[56].

FINDING SUMMARY
FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[57]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[57-58]. Alterations such as seen here may disrupt FBXW7 function or expression[58-65].

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GENE
STK11

ALTERATION
L85*

TRANSCRIPT ID
NM_000455

CODING SEQUENCE EFFECT
254T>A

POTENTIAL TREATMENT STRATEGIES

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)[66], 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%%)[66-67], although a case study reported ongoing response for 1 patient with KRAS/STK11 co-mutations treated with nivolumab and ipilimumab[68]. 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)[69]. 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[70-71] . 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[72-73] or anti-PD-1 therapy[74]. Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[75-79]. Case studies have reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus[80], with 1 PR observed in a PJS patient for 9 months until progression[80]. 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[81]. In one preclinical study, STK11 loss was associated with sensitivity to combination treatment including an SRC inhibitor[82]; however, the clinical relevance of these findings has not been established.

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%)[54,76,83-87]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases[55] and was not observed in any of 178 lung squamous cell carcinoma cases[54]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations[85-86]. 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[76]. 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[88].

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[75]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[82,89]. Alterations such as seen here may disrupt STK11 function or expression[90-101].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[102]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[102-104]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[102-104], and individuals with this syndrome have a 30-50% risk of developing breast cancer[102,104]. 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
BRAF

ALTERATION
K601N

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1803A>T

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data suggest that BRAF activating alterations such as activating mutations or fusions may confer sensitivity to multikinase inhibitors that have activity against BRAF, such as sorafenib[105-110] and regorafenib[111-113]; MEK inhibitors, such as trametinib[114-122], selumetinib[123-125], binimetinib[126-127], and cobimetinib[128-130]; and ERK inhibitors[131]. Additionally, inhibition of HSP90 leads to the degradation of oncogenic proteins, such as BRAF, which suggests that HSP90 inhibitors may be effective in malignancies with activating BRAF mutations; indeed, combinations of BRAF or MEK inhibitors with other therapies, including HSP90 inhibitors, immunotherapies, PI3K/AKT inhibitors, ERK inhibitors, and/or CDK4/6 inhibitors, are being tested in clinical trials[132-134]. Although limited preclinical data suggest that BRAF K601E may be sensitive to the BRAF-mutant-selective inhibitor vemurafenib[135], patients with BRAF K601E have not benefited from V600-targeted inhibitors in clinical studies, with no response for any of 17 patients treated with vemurafenib (6 SDs, 5 PDs, and 7 outcomes not specified)[136-140] nor for 2 patients treated with dabrafenib (1 SD, 1 PD)[141], and rapid disease progression observed in 2 patients treated with combination dabrafenib and trametinib[137]. A Phase 2 trial of selumetinib reported partial response (PR) in 32% (8/25) of pediatric patients with BRAF-mutant pilocytic astrocytoma, including 2 with BRAF V600E and 6 with a KIAA1549-BRAF fusion[124]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs in 3/19 previously treated and 1/2 newly diagnosed patients with BRAF V600E-mutant melanoma, 3/12 patients with BRAF-mutant lung cancer (2 with V600E and 1 with L597Q), and 4/21 patients with other BRAF-mutant cancers (2 with G469A, 1 with V600E, and 1 with L485W); 2 patients with BRAF V600E mutations also experienced CNS response[142]. 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

BRAF mutations have been reported in up to 4% of non-small cell lung cancer (NSCLC) cases in various studies[143-147], with a large-scale meta-analysis suggesting a frequency of 3%[148]. BRAF mutations are significantly more prevalent in lung adenocarcinoma than non-adenocarcinoma NSCLC[145,148]. BRAF mutations can co-occur with alterations in other known oncogenic drivers of NSCLC, including EGFR, KRAS, and ALK[145,147]. Studies have reported a lack of association between BRAF mutation and tumor stage or prognosis in NSCLC[143,148]. Unlike BRAF V600 mutations, responses for patients with NSCLC and non-V600 mutations to BRAF-specific inhibitors such as vemurafenib and dabrafenib have been limited (1 partial response, 1 stable disease, 6 progressive disease and two additional unspecified non-responses)[136,149-150].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[151-152]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[153-154]. The BRAF K601E mutation has been characterized as activating, driving robust MEK activation upon transfection into cells[155-156]. Other mutations at this codon, including K601T and K601N, have been observed in the context of cancer but have not been characterized for their effect on protein function or response to BRAF-targeted therapies.

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GENE
KRAS

ALTERATION
G12R

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
34G>C

POTENTIAL TREATMENT STRATEGIES

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[157-162]. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[163-165]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the PFS or OS of patients with KRAS-mutant NSCLC relative to docetaxel alone[166]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[167]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[168-170] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[171-172], RAF[173], pan-ERBB[174], or BCL2[175-176]. However, a Phase 1 combination trial of the MEK inhibitor PD-0325901 with the CDK4/6 inhibitor palbociclib that included 17 patients with KRAS-mutant NSCLC reported 1 PR, >50% SD, and 5 patients with PFS >6 months; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among patients with tumors harboring KRAS mutation and STK11 inactivation[177]. The CDK4/6 inhibitor abemaciclib demonstrated increased activity in KRAS-mutated NSCLC compared to KRAS-wildtype NSCLC (median PFS of 2.8 vs. 1.9 months) in a Phase 1 trial[178] but did not prolong median OS compared to erlotinib (7.4 vs. 7.8 months, HR=0.97), in spite of improved PFS (3.6 vs. 1.9 months, HR=0.58) and ORR (8.9% vs. 2.7%) relative to erlotinib, in a Phase 3 study for patients with platinum-refractory KRAS-mutated advanced NSCLC[179]. Although some studies have suggested that KRAS mutation status may predict a lack of response to the EGFR inhibitors erlotinib and gefitinib in patients with lung cancer, a retrospective study suggests that there is no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wildtype and KRAS-mutated patients[180-183]. A study assessing the immune checkpoint inhibitor nivolumab for pretreated patients with KRAS-mutated (n=206) or KRAS-wildtype (n=324) advanced NSCLC observed a similar ORR (20% vs. 17%), median PFS (4 vs. 3 months) and OS (11.2 vs. 10 months) in both cohorts, although the 3-month PFS rate was significantly longer in KRAS-positive than KRAS-negative patients (53% vs. 42%)[184]. Co-occurring KRAS and STK11 alterations are associated with poorer response to immune checkpoint inhibitors for patients with NSCLC. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS- and STK11-mutated tumors than for those whose KRAS-mutated tumors were STK11-wildtype (6.4 vs. 16.1 months, HR=1.99), as well as markedly fewer objective responses for patients with KRAS-/STK11-mutated versus KRAS-/TP53-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])[66] and GEMINI (0% [0/6], vs. 53% [9/17])[185]. Another study observed that patients with NSCLC and KRAS-mutated tumors without STK11 alteration who were treated with second-line immunotherapy experienced similar median PFS (2.8 vs. 2.2 months, HR = 1.64) and numerically longer median OS (7.7 vs. 3.5 months, HR = 2.3; p=0.09) compared to patients harboring mutations in both KRAS and STK11[186]. Combination of a RAF-MEK inhibitor CH5126766 and FAK inhibitor defactinib elicited clinical responses for patients with low-grade serous ovarian cancer (PR rate 50% [4/8]) and non-small cell lung cancer (PR rate 10% [1/10]) with KRAS mutations[187]. The reovirus Reolysin targets cells with activated RAS signaling[188-190] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[191-199]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[200].

FREQUENCY & PROGNOSIS

Studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 27-37% of lung adenocarcinomas[55,87,201-210], 10.5-33% of lung adenosquamous carcinomas[211-213], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[214]. KRAS mutation was associated with shorter PFS (7.0 vs. 8.6 months, p=0.026) and OS (14.2 vs. 21.6 months, p=0.019) with first-line treatment with bevacizumab plus chemotherapy in a retrospective study[215] and a lower major pathological response rate (0% [0/10] vs. 35.5% [11/31]) after neoadjuvant bevacizumab plus chemotherapy followed by adjuvant bevacizumab in a Phase 2 trial[216], relative to those patients lacking KRAS mutation. However, addition of atezolizumab to first-line bevacizumab and chemotherapy improved PFS regardless of KRAS status in the Phase 3 IMpower150 study (HR=0.50 for KRAS mutant vs. 0.47 for KRAS wild-type vs. 0.67 for KRAS unknown)[217]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[218]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior[204,210,219]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[220].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[158,221]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, and K117N have been characterized as activating and oncogenic[158,222-243].

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GENE
APC

ALTERATION
rearrangement exon 16

POTENTIAL TREATMENT STRATEGIES
There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[244]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[245-246]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[247].

FREQUENCY & PROGNOSIS
In the TCGA datasets, APC mutations have been reported in 3.9% of lung adenocarcinomas[55] and 4.5% of lung squamous cell carcinoma samples analyzed[54]. Studies of APC in lung cancer have reported mutations in 5-7% of non-small cell lung cancer (NSCLC) tumors examined[201,248]. In contrast, loss of heterozygosity at the APC/MCC locus has been reported in up to 68% (17/25) of NSCLC, with a higher incidence in squamous cell carcinomas compared to adenocarcinomas[249-250]. Hypermethylation of APC in NSCLC tumors has been reported in a number of studies[251-254]; hypermethylation and lower APC mRNA expression have been associated with poorer survival in patients with NSCLC[250,255].

FINDING SUMMARY
APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[256]. Alterations such as seen here may disrupt APC function or expression[257-261].

POTENTIAL GERMLINE IMPLICATIONS
Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[262-264]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[265], and in the appropriate clinical context germline testing of APC is recommended.

GENE
ATRX

ALTERATION
S1125fs*28, inversion exons 3-9, L767fs*1

TRANSCRIPT ID
NM_000489, NM_000489

CODING SEQUENCE EFFECT
3373_3490>CTGAAT, 2300_2397>AAC

POTENTIAL TREATMENT STRATEGIES
No targeted therapies are available to address ATRX inactivation. Although ATR inhibition is being investigated as a potential therapeutic approach in the context of ALT, a preclinical study demonstrated that ATRX inactivation is not sufficient to confer sensitivity to ATR inhibitors[266]. However, ATRX-deficient GBM cells were sensitive to the double-strand break-inducing agents doxorubicin, irinotecan, and topotecan but not single-strand break-inducing agents such as temozolomide[267]. Preclinical evidence suggests that ATRX may be required for CDK4/6 inhibitors to be most effective[268].

FREQUENCY & PROGNOSIS
Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[269]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[269-271], 12.6% of pheochromocytomas and paragangliomas[272], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[273-277]. ATRX loss in PNET[270,278] and melanoma[279] and mutation in other neuroendocrine tumors[272] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[267]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[280-283] and has been proposed as a distinguishing biomarker[281-283]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[274-277]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[281]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[284-285].

FINDING SUMMARY
ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[286-287]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[269,285,288-289]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[290-292]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[266,286]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[293].

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GENE
CDKN2A/B

ALTERATION
p16INK4a Y44fs*1

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
131_132insA

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[294-297]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[298-299], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[300-306]; it is not known whether CDK4/6 inhibitors would be beneficial in this case.

FREQUENCY & PROGNOSIS
CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[55]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[54]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[54,307-312]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[309,313-315].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[316-317]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[308,318]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[319-320]. One or more alterations observed here are predicted to result in p16INK4a loss of function[321-342].

POTENTIAL GERMLINE IMPLICATIONS
Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[343]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[344-345]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[346-348]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[349-351]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
CREBBP

ALTERATION
R1446C

TRANSCRIPT ID
NM_004380

CODING SEQUENCE EFFECT
4336C>T

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in CREBBP. The use of histone deacetylase (HDAC) inhibitors are being investigated in clinical trials that are recruiting patients with either lymphoma or urothelial carcinoma harboring CREBBP alterations. However, it has been reported that there is no correlation between CREBBP mutation status and response to HDAC inhibitors in DLBCL[352].

FREQUENCY & PROGNOSIS
CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 39%) and diffuse large B-cell lymphoma (DLBCL, 17%), and at lower frequency in acute lymphoblastic leukemia (ALL, 6%), and tumors of the urinary tract (15%), skin (11%), endometrium (9%), liver (9%), and stomach (9%) (COSMIC, 2021)[353]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[354], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[355]. Reports have found CREBBP mutation in 62-68% of patients with FL[356-357], which was associated with immune evasion[356]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[358-359].

FINDING SUMMARY
CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[360]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[361]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[362-363].

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GENE
DNMT3A

ALTERATION
R882H, Y481*, P904L, splice site 1015-1G>T, R635Q

TRANSCRIPT ID
NM_022552, NM_022552, NM_022552, NM_022552, NM_022552

CODING SEQUENCE EFFECT
2645G>A, 1443C>A, 2711C>T, 1015-1G>T, 1904G>A

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS
DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[364-365]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021). 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[366-371]. 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[366-367]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[372]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[370,373-374]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY
The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[375-376]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[253,377-381]. Mutations at codon 882, including R882S, R882H, and R882C, have demonstrated reduced methyltransferase activity in vitro, with R882H and R882C conferring increased cell proliferation[382-384]. About half of all DNMT3A mutations in AML are R882H, which leads to a partially defective enzyme and altered oligomerization behavior, although the effect on global methylation remains to some extent controversial; in addition, at least one report suggests that mutation of R882 is associated with sensitivity to DNA methyltransferase inhibitors[382-385]. On the basis of this, any alteration at R882 is likely to promote tumorigenesis, although the efficacy of DNMT inhibitors may not be consistent for all mutations. Alterations such as seen here may disrupt DNMT3A function or expression[386-389]. Although alterations such as R635Q 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
KEL

ALTERATION
splice site 1593-1G>T

TRANSCRIPT ID
NM_000420

CODING SEQUENCE EFFECT
1593-1G>T

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to target genomic alterations in KEL.

FREQUENCY & PROGNOSIS
KEL mutations have been reported in tumors of the skin, lung, endometrium, stomach, large intestine, soft tissue, and liver at rates of 1.9-8.4%; up to 1.2% of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphocytic leukemia-small lymphocytic lymphoma (CLL/SLL) samples (COSMIC, 2021)[353]. However, the mechanism by which KEL mutations contribute to tumor formation is not known.

FINDING SUMMARY
KEL encodes a transmembrane glycoprotein with similarities to zinc-dependent metalloproteases; this glycoprotein is highly polymorphic and forms the Kell blood group antigen[390].

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GENE
NKX2-1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies or trials that target tumors with TTF-1 amplification or overexpression. Lung cancer cell lines that express both TTF-1 and NKX2-8, which is located in the same amplicon as NKX2-1, have demonstrated resistance to cisplatin therapy[391], although conflicting data has also been reported[392].

FREQUENCY & PROGNOSIS
Putative amplification of NKX2-1 has been reported with the highest incidence in lung cancer, and has been observed in 14% of adenocarcinomas[55] and 5% of squamous cell carcinomas (SCC)[54] as well as other tumor types including prostate adenocarcinomas (6%)[393], and poorly differentiated and anaplastic thyroid cancers (4%)[394]. NKX2-1 mutation has been observed in 9% of acinar cell carcinomas of the pancreas[395], 5% of uterine carcinosarcomas[396], and is infrequent in other tumor types (cBioPortal, COSMIC, 2021)[353,364-365]. TTF-1 is expressed in a majority of lung adenocarcinomas and small cell carcinomas, as well as in a subset of thyroid and CNS tumors[397-399]. Cytoplasmic TTF-1 expression has been reported as an adverse prognostic factor in breast carcinoma[400-401]. However, whether amplification and/or expression status of NKX2-1 have prognostic implications for patients with lung cancer is controversial[391-392,402-405]. TTF-1 has been observed to have tumor-promoting as well as anti-oncogenic roles[406-407].

FINDING SUMMARY
NKX2-1 (NK2 homeobox 1) encodes the thyroid transcription factor TTF-1[408]. Amplification of NKX2-1 results in overexpression of TTF-1 and upregulated transcription of downstream target genes[409].

GENE
SMARCA4

ALTERATION
splice site 2973+1G>C

TRANSCRIPT ID
NM_003072

CODING SEQUENCE EFFECT
2973+1G>C

POTENTIAL TREATMENT STRATEGIES
Clinical[410] and preclinical[411-417] data suggest that patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with EZH2 inhibitors, including tazemetostat. In addition, preclinical data have demonstrated that SMARCA4-deficient non-small cell lung cancer (NSCLC) and SCCOHT patient-derived xenografts and cell lines are highly sensitive to CDK4/6 inhibition through a synthetic lethal mechanism of reduced cyclin D1 expression[418-419]. Notably, similar drug sensitivity was detected in SMARCA4-deficient lung and ovarian tumors, thereby suggesting that SMARCA4-deficient tumors are likely to be sensitive to CDK4/6 inhibition regardless of tissue of origin[418-419]. Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[420]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[421]. 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, SMARCA4 mutations have been reported in 6% of lung adenocarcinomas[55] and in 5% of lung squamous cell carcinomas[54]. Loss of BRG1 protein expression has been observed in 10-15% of non-small cell lung cancer (NSCLC) cases in the scientific literature[422-424]. Loss of expression of BRG1 and BRM, another catalytic subunit in SWI/SNF chromatin remodeling complexes, has been correlated with poor prognosis in patients with NSCLC[422-423,425-426].

FINDING SUMMARY
SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[427]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[428]. 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.

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GENE
TP53

ALTERATION
S241C, P152L, G245V, G154V

TRANSCRIPT ID
NM_000546, NM_000546, NM_000546, NM_000546

CODING SEQUENCE EFFECT
722C>G, 455C>T, 734G>T, 461G>T

POTENTIAL TREATMENT STRATEGIES

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[429-432], or p53 gene therapy and immunotherapeutics such as SGT-53[433-437] and ALT-801[438]. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[439]. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[440]. 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 in patients with platinum-refractory TP53-mutated ovarian cancer[441]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[442]. 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[443]. 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[444]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[437]. 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[445]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[446-448]. In a Phase 1b trial in 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[449]. 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[450-451]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[452-453]. 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)[54-55,311,454-458], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[54-55,87,459]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[364-365]. 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[218]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[460]. 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[366-371]. 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[366-367]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[372]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[370,373-374]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[461]. Alterations such as seen here may disrupt TP53 function or expression[462-466].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2020)[467]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[468-470], including sarcomas[471-472]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[473] to 1:20,000[472]. 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[474]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Atezolizumab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, triple-negative breast 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[1-3,475] , 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 (28.6% 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[476]. 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[477]. 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[1,478] . In the Phase 3 IMpower131 study, addition of atezolizumab to first-line carboplatin and paclitaxel improved median PFS for patients with squamous NSCLC compared with chemotherapy alone (6.3 vs. 5.6 months, HR=0.71); longer PFS was observed across PD-L1 expression subgroups[479]. 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[217,480-481] . 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[480]. 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[217]. 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[481]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38.3% vs. 28.6%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[477]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[482], confirming previous Phase 2 trial data[483-484] . Clinical benefit was observed for patients regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[482]. Retrospective analysis of the OAK trial revealed numerically improved ORR for patients receiving concomitant atezolizumab and metformin compared with atezolizumab alone (25% vs. 13%), but no difference in PFS or OS with the addition of metformin[485].

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Cemiplimab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data[1-3,475] , 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[486]. 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])[487].

Durvalumab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data[1-3,475] , 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%[475]. In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable NSCLC who did not have progression on chemoradiotherapy (CT), durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; PFS was 17.8 versus 5.6 months (HR=.46) for patients with PD-L1 expression ≥1%, and 10.7 versus 5.6 months (HR=.73) for patients with PD-L1 expression <1%. OS benefit was observed for patients with PD-L1 expression ≥1% (not reached [NR] vs. 29.6 months, HR=0.59), but not for those with PD-L1 expression <1% (33.1 vs. 45.6 months, HR=1.14)[488]. 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 investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[489]. 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%)[489]. 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 and 0.85, respectively); however, patients with bTMB ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[490]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[491-492] and OS[491] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 30.9% (21/68), compared with ORRs of 16.4% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity, respectively[492]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR- or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25.0% (10/40) of patients[493].

Nivolumab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved 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, hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), and esophageal squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,475] , 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 (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)[494]. In advanced squamous NSCLC, second-line nivolumab resulted in longer median OS (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[495-496] . 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 13.4% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[497]. Combination of nivolumab with the CTLA4-targeting antibody ipilimumab improved median OS for patients with advanced NSCLC relative to chemotherapy regardless of PD-L1 positivity, TMB status (17.1 vs. 13.9 months, HR=0.73), or brain metastases (18.8 vs. 13. 7 months, HR=0.57) in the Phase 3 CheckMate 227 study[498-499] , despite earlier analysis of this trial which suggested improved PFS only for patients with TMB ≥10 muts/Mb[500]. In another arm of the CheckMate 227 study, combination of nivolumab with platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[501], despite Phase 1 results in the same setting suggesting improved ORR and OS[502].

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Pembrolizumab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data[1-3,475] , 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 for the first-line treatment of patients with PD-L1-positive 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)[503] and ≥50% (26.3 vs. 13.4 months, HR=0.62–0.69)[504], with estimated 5-year OS rates of 31.9% vs 16.3% in the KEYNOTE-024 study[504]. 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 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[505]. 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 90% to 100% relative to those with TPS 50% to 89% (not reached vs. 15.9 months, HR=0.39)[506]. 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)[507] or squamous (KEYNOTE-407)[508-509] NSCLC, regardless of PD-L1 or TMB status[510]; exploratory analysis of KEYNOTE-189 demonstrated superiority of the pembrolizumab combination therapy regardless of bTMB status[511]. 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 (+21.5%, p=0.011)[512]. 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[513]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single-agent and in combination with chemotherapy, for the treatment of patients with NSCLC and brain metastases[514-516] . Clinical activity has also been achieved with pembrolizumab in combination with ipilimumab[517], the HDAC inhibitor vorinostat[518], and the multikinase inhibitor lenvatinib[519].

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Avelumab

Assay findings association

Blood Tumor Mutational Burden
18 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data[1-3,475] , 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 a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the ORR was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median PFS was 12 weeks for both cohorts[520-521]. In patients with NSCLC and PD-L1-positive tumor cells, first-line treatment with avelumab resulted in numerically increased ORR (20%; 7/35 vs. 0%; 0/10) and a trend toward prolonged PFS (11.6 vs. 6.0 weeks) relative to patients with fewer than 1% of tumor cells expressing PD-L1[520]; however, response rates, PFS, and OS were similar regardless of immune or tumor cell PD-L1 expression in patients who had previously received platinum-based treatment[521].

Everolimus

Assay findings association

FBXW7
Q41*

STK11
L85*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on strong clinical evidence from studies of several patients with lung, renal, liver, and other cancers[36-38] and extensive preclinical evidence[39-41] , FBXW7 loss or inactivation may predict sensitivity to mTOR inhibitors such as everolimus. Specifically, in one study of patients with different tumor types, 7/10 patients with FBXW7-mutated tumors treated with various mTOR inhibitors achieved stable disease for 2.2-6.8+ months; the patient who showed the best response carried an FBXW7 mutation as the only detectable mutation[37]. Increased mTOR signaling is present in LKB1-deficient tumors[75-77,79,522] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[75]. Everolimus elicited clinical responses lasting >6 months in 2 patients with pancreatic cancer[80,523] and 1 patient with atypical pituitary adenoma[524], all of whom harbored STK11 alterations in their tumors.

SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[525], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[526]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the combinations produced 1 CR and 10 PRs (n=52), although treatments were not well tolerated[527]. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing SD (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses[528-529] . A trial of combination treatment with sorafenib and everolimus reported 1 PR and 1 SD in 2 patients with lung adenocarcinoma, with both patients experiencing progression-free survival of more than 4 months[530]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[170], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[531].

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Temsirolimus

Assay findings association

FBXW7
Q41*

STK11
L85*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on strong clinical evidence from studies of several patients with lung, liver, and other cancers[36-37] and extensive preclinical evidence[39-41] , FBXW7 loss or inactivation may predict sensitivity to mTOR inhibitors such as temsirolimus. Increased mTOR signaling is present in LKB1-deficient tumors[75-77,79,522] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[75].

SUPPORTING DATA

In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point[532]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited PR and 2 exhibited SD[533].

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.

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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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

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

18 Muts/Mb

RATIONALE

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

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: Verona (Italy), Padova (Italy), Bergamo (Italy), Monza (Italy), Milano (Italy), Innsbruck (Austria), Rankweil (Austria), Immenstadt im Allgäu (Germany), Graz (Austria), Toulon Cedex 9 (France)

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: Brescia (Italy), Monza (Italy), Milano (Italy), Rozzano (Italy), Meldola (Italy), Orbassano (Italy), Esslingen (Germany), Roma (Italy), Strasbourg (France), Toulon (France)

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: Padova (Italy), Monza (Italy), Milano (Italy), Rozzano (Italy), St. Gallen (Switzerland), Orbassano (Italy), Sant'Andrea Delle Fratte (PG) (Italy), Basel (Switzerland), Lausanne (Switzerland), Wels (Austria)

NCT03516981

PHASE 2

A Study of Biomarker-Directed, Pembrolizumab (MK-3475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (MK-3475-495/KEYNOTE-495)

TARGETS
CTLA-4, LAG3, PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Legnago (Italy), Rozzano (Italy), Meldola (Italy), Chur (Switzerland), Siena (Italy), St. Gallen (Switzerland), Orbassano (Italy), Zuerich (Switzerland), Basel (Switzerland), Roma (Italy)

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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: Brescia (Italy), Monza (Italy), Lucca (Italy), St.Gallen (Switzerland), Kempten (Germany), Zuerich (Switzerland), Perugia (Italy), Basel (Switzerland), Lausanne (Switzerland), Gerlingen (Germany)

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Padova (Italy), Siena (Italy), Pierre Benite (France), Marseille (France), Napoli (Italy), Villejuif (France), Lille (France), Barcelona (Spain), Hospitalet de Llobregat (Spain), Poznan (Poland)

NCT03823625

PHASE 2

An Open-label, Randomized, Parallel, Non Comparative, Phase II Trial of Nivolumab Plus Ipilimumab Versus Platinum-based Chemotherapy Plus Nivolumab in Chemonaive Metastatic or Recurrent Squamous-Cell Lung Cancer (SqLC)

TARGETS
PD-1, CTLA-4

LOCATIONS: Negrar (Italy), Padova (Italy), Reggio Emilia (Italy), Modena (Italy), Milano (Italy), Ravenna (Italy), Meldola (Italy), Rimini (Italy), Perugia (Italy)

NCT03656718

PHASE 1/2

A Study of Subcutaneous Nivolumab Monotherapy With or Without Recombinant Human Hyaluronidase PH20 (rHuPH20)

TARGETS
PD-1

LOCATIONS: Padova (Italy), Rozzano (Italy), Maastricht (Netherlands), Villejuif (France), Amsterdam (Netherlands), Saint Herblain (France), Warszawa (Poland), Whitchurch (United Kingdom), Madrid (Spain), Wirral (United Kingdom)

NCT03976518

PHASE 2

Atezolizumab in Advanced Non-small Cell Lung Cancer With Rare Histologies (CHANCE Trial)

TARGETS
PD-L1

LOCATIONS: Padova (Italy), Parma (Italy), Bologna (Italy), Milano (Italy), Udine (Italy), Pisa (Italy), Orbassano (Italy), Perugia (Italy), Cuneo (Italy), Roma (Italy)

NCT01968109

PHASE 1/2

Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors

TARGETS
PD-1, LAG-3

LOCATIONS: Padova (Italy), Milano (Italy), Zurich (Switzerland), Lausanne (Switzerland), Heilbronn (Germany), Pierre Benite Cedex (France), Wuerzburg (Germany), Marseille Cedex 5 (France), Wien (Austria), Napoli (Italy)

GENE
BRAF

ALTERATION
K601N

RATIONALE
BRAF activating alterations may predict sensitivity to inhibition of the MAPK pathway by agents such as RAF inhibitors and MEK inhibitors. 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.

NCT02974725

PHASE 1

Study of LXH254 and LTT462 in NSCLC

TARGETS
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

LOCATIONS: Verona (Italy), Milano (Italy), Rozzano (Italy), Paris Cedex 10 (France), Heidelberg (Germany), Frankfurt (Germany), Napoli (Italy), Dresden (Germany), Koeln (Germany), Essen (Germany)

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Seongnam (Korea, Republic of), Hwasun (Korea, Republic of), Pusan (Korea, Republic of)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03520842

PHASE 2

Regorafenib and Methotrexate in Treating Participants With Recurrent or Metastatic KRAS Mutated Non-Small Cell Lung Cancer

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: California

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT04200404

PHASE 1/2

A Study of CS1001 in Subjects With Advanced or Refractory Solid Tumors

TARGETS
BRAF, KIT, RET, VEGFRs, PD-L1

LOCATIONS: Kurralta Park (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Nedlands (Australia), Melbourne (Australia), Blacktown (Australia), Randwick (Australia)

NCT03155620

PHASE 2

Pediatric MATCH: Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Advanced Refractory Solid Tumors or Lymphomas

TARGETS
TRKA, TRKB, TRKC, FGFRs, EZH2, mTOR, PI3K, MEK, ABL, ALK, AXL, MET, ROS1, BRAF, PARP, Farnesyl transferase, CDK4, CDK6, ERK2, ERK1, RET

LOCATIONS: Maine, Massachusetts, New Hampshire, Vermont, Rhode Island, Connecticut, New York

NCT03475251

PHASE 1

A Study of CS1003 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, BRAF, KIT, RET, VEGFRs

LOCATIONS: Randwick (Australia)

GENE
FBXW7

ALTERATION
Q41*

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

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: Innsbruck (Austria), Salzburg (Austria), Heidelberg (Germany), Wien (Austria), Köln (Germany), Villejuif (France), Paris (France), Bordeaux (France), Nantes Cedex 1 (France), Montreal (Canada)

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

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)

NCT02389309

PHASE 1

A Trial of Dasatinib (PDGFR and SRC Inhibitor), Temsirolimus and Cyclophosphamide in Patients With Advanced Solid Tumors

TARGETS
mTOR, ABL, DDR2, KIT, SRC

LOCATIONS: Texas

NCT03245151

PHASE 1/2

Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors

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

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, District of Columbia, Virginia, Michigan, Ohio, Indiana

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: New York, New Jersey, Maryland

GENE
KRAS

ALTERATION
G12R

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Clinical evidence suggests that patients with KRAS-mutant NSCLC may be sensitive to the CDK4/6 inhibitor abemaciclib.

NCT02974725

PHASE 1

Study of LXH254 and LTT462 in NSCLC

TARGETS
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

LOCATIONS: Verona (Italy), Milano (Italy), Rozzano (Italy), Paris Cedex 10 (France), Heidelberg (Germany), Frankfurt (Germany), Napoli (Italy), Dresden (Germany), Koeln (Germany), Essen (Germany)

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Besançon (France), Paris (France), Marseille (France), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Plerin Sur Mer (France), København Ø (Denmark), Herlev (Denmark), Madrid (Spain), Pozuelo de Alarcón (Spain)

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Seongnam (Korea, Republic of), Hwasun (Korea, Republic of), Pusan (Korea, Republic of)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Nedlands (Australia), Melbourne (Australia), Blacktown (Australia), Randwick (Australia)

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NCT03170206

PHASE 1/2

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer

TARGETS
MEK, CDK4, CDK6

LOCATIONS: Massachusetts

NCT03581487

PHASE 1/2

Durvalumab, Tremelimumab, and Selumetinib in Treating Participants With Recurrent or Stage IV Non-small Cell Lung Cancer

TARGETS
MEK, PD-L1, CTLA-4

LOCATIONS: Texas

NCT02644460

PHASE 1

Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors

TARGETS
CDK4, CDK6

LOCATIONS: Georgia, Colorado, Arizona

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: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

GENE
STK11

ALTERATION
L85*

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

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: Innsbruck (Austria), Salzburg (Austria), Heidelberg (Germany), Wien (Austria), Köln (Germany), Villejuif (France), Paris (France), Bordeaux (France), Nantes Cedex 1 (France), Montreal (Canada)

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

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)

NCT02389309

PHASE 1

A Trial of Dasatinib (PDGFR and SRC Inhibitor), Temsirolimus and Cyclophosphamide in Patients With Advanced Solid Tumors

TARGETS
mTOR, ABL, DDR2, KIT, SRC

LOCATIONS: Texas

NCT03245151

PHASE 1/2

Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors

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

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, District of Columbia, Virginia, Michigan, Ohio, Indiana

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: New York, New Jersey, Maryland

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.

AKT3
H351N

ALK
G1287A

ATM
L2307F

ATR
R1951L

ATRX
D1120Y, D611H, D678H, D732H, D848H, D896N, D981Y, E683K, E723D, E884D and G628A

CARD11
L267V, S222C and rearrangement

DOT1L
Q737fs*30

ERBB3
S1097P

FGF14
T99N

KEL
P76H

MUTYH
S284I

NPM1
E170_E174del

NTRK3
D527E

PIK3C2G
P188fs*11 and P758S

POLE
A1093fs*1

RBM10
A324P

SDHA
A466T and S456L

SNCAIP
L9F

TSC1
M322T

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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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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** (MEK1) Exons 2, 3	***MAP2K2*** (MEK2) Exons 2-4, 6, 7	*MAP2K4*	*MAP3K1*	*MAP3K13*

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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.

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*	*WTI*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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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 detects select genomic rearrangements, select copy number alterations, 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 ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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

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to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not 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 with no conflicts), 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 *BAP1, BRCA1, BRCA2, BRIP1, 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.

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®.

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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 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 3.0.0

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