PATIENT	**TUMOR TYPE** Lung non-small cell lung carcinoma (NOS)	**REPORT DATE** 09 Feb 2022	
	COUNTRY CODE PE	**ORDERED TEST #** ORD-1293721-01	

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

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
DATE OF BIRTH 28 June 1950
SEX Female
MEDICAL RECORD # Not given

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

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID 20-2305-9
SPECIMEN TYPE Block
DATE OF COLLECTION 23 December 2020
SPECIMEN RECEIVED 28 January 2022

Biomarker Findings
Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

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

KRAS G12V

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, EGFR, ERBB2, MET, RET, ROS1*

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† See About the Test in appendix for details.

Report Highlights
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 5)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: *KRAS G12V* (p. 3)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS - G12V	none	none
10 Trials see p. 5		

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

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

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BIOMARKER FINDINGS

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BIOMARKER
Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER
Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others)[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. 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)[44]. 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[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].

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GENE
KRAS

ALTERATION
G12V

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>T

VARIANT ALLELE FREQUENCY (% VAF)
22.8%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[64-69]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[70]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study[71-72]. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[73-74]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[75]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[76]. 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[77-79]. 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[80]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[81]. 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[82-84] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[85-86], RAF[87], pan-ERBB[88], or BCL2[89-90]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[91-92]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[93-94]. 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[95]. 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[96] 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[97]. 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[98-101]. 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%)[102]. 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])[103] and GEMINI (0% [0/6], vs. 53% [9/17])[104]. 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[105].

FREQUENCY & PROGNOSIS
Studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 27-37% of lung adenocarcinomas[47-48,106-115], 10.5-33% of lung adenosquamous carcinomas[116-118], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[119]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior (NCCN NSCLC Guidelines, v1.2022)[109,115,120]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[121]. 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[122] 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[123], 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)[124]. 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[125].

FINDING SUMMARY
KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes

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GENOMIC FINDINGS

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can cause uncontrolled cell proliferation and tumor formation[65,126]. 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, R68S, and K117N have been characterized as activating and oncogenic[65,127-149].

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CLINICAL TRIALS

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GENE
KRAS

ALTERATION
G12V

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual 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.

NCT03600701 — PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: Florida, Alabama, North Carolina, Virginia, District of Columbia, Oklahoma, Ohio, Michigan, New Hampshire

NCT03989115 — PHASE 1/2

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

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

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: Florida, North Carolina, Connecticut, Minnesota, Nevada, California, Malaga (Spain), Pozuelo de Alarcón (Spain), Madrid (Spain), Plerin Sur Mer (France)

NCT04801966 — PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

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

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CLINICAL TRIALS

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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, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic
Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2,
MDM2, ADORA2A

LOCATIONS: Tennessee, Ohio, Nevada, Malaga (Spain), Madrid (Spain), Valencia (Spain), Pamplona (Spain), Saint Herblain (France), Barcelona (Spain),
Toulouse (France)

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
BCL2, BCL-XL, BCL-W, MEK

LOCATIONS: Massachusetts

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

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, ROS1, AXL, TRKA, MET,
TRKC, MEK, AKTs, EGFR, PD-L1, KIT,
DDR2, VEGFRs, PDGFRA, FLT3, RET,
TRKB

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

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APPENDIX   Variants of Unknown Significance

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.

BRCA2	*KLHL6*	*NPM1*	*RNF43*
Y3098H	R345C	Q209H	P594L

SMAD4	*SPOP*	*TET2*	*TSC1*
W524S	K103*	L1667M	K587R

Electronically signed by Erik Williams, M.D. | 09 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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APPENDIX   Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA
**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

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

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

Ranking of Therapies and Clinical Trials
Ranking of Therapies in Summary Table
Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION
Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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

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PATIENT

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Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.

5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 1,091x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
7. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
8. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
9. Zang YS, et al. Cancer Med (2019) pmid: 31270941
10. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
11. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
12. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
13. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
14. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
15. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
31. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
32. Rizvi NA, et al. Science (2015) pmid: 25765070
33. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
34. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
35. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
36. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
37. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
38. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
39. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
40. Paz-Ares et al., 2019; ESMO Abstract LBA80
41. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
42. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
43. Spigel et al., 2016; ASCO Abstract 9017
44. Xiao D, et al. Oncotarget (2016) pmid: 27009843
45. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
46. Govindan R, et al. Cell (2012) pmid: 22980976
47. Ding L, et al. Nature (2008) pmid: 18948947
48. Imielinski M, et al. Cell (2012) pmid: 22980975
49. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
50. Stein et al., 2019; DOI: 10.1200/PO.18.00376

51. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
52. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
53. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
54. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
55. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
56. Johnson BE, et al. Science (2014) pmid: 24336570
57. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
58. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
59. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
60. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
61. Nature (2012) pmid: 22810696
62. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
63. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
64. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
65. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
66. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
67. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
68. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
69. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
70. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
71. Krebs et al., 2021; AACR Abstract CT019
72. Shinde et al., 2020; AACR Abstract CT143
73. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
74. Mainardi S, et al. Nat Med (2018) pmid: 29808006
75. Koczywas et al., 2021; AACR Abstract LB001
76. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
77. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
78. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
79. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
80. Jänne PA, et al. JAMA (2017) pmid: 28492898
81. Gandara DR, et al. J Thorac Oncol (2017) pmid: 27876675
82. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
83. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
84. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
85. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
86. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
87. Lamba S, et al. Cell Rep (2014) pmid: 25199829
88. Sun C, et al. Cell Rep (2014) pmid: 24685132
89. Hata AN, et al. Cancer Res. (2014) pmid: 24675361
90. Tan N, et al. Mol. Cancer Ther. (2013) pmid: 23475955
91. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) pmid: 30683722
92. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
93. Hofmann et al., 2021; AACR Abstract CT210
94. Gort et al., 2020; ASCO Abstract TPS3651
95. Shapiro et al., 2017; AACR Abstract CT046
96. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
97. Goldman et al., 2018; ASCO Abstract 9025
98. Mao C, et al. Lung Cancer (2010) pmid: 20022659
99. Sun JM, et al. PLoS ONE (2013) pmid: 23724098
100. Pao W, et al. PLoS Med. (2005) pmid: 15696205

101. Ludovini V, et al. J Thorac Oncol (2011) pmid: 21258250
102. Passiglia F, et al. Br. J. Cancer (2019) pmid: 30377342
103. Skoulidis F, et al. Cancer Discov (2018) pmid: 29773717
104. Skoulidis et al., 2017; IASLC 17th World Congress on Lung Cancer Abstract MA04.07
105. Marmarelis et al., 2018, IASLC WCLC Abstract P1.01-64
106. Nature (2014) pmid: 25079552
107. Aviel-Ronen S, et al. Clin Lung Cancer (2006) pmid: 16870043
108. Villaruz LC, et al. Cancer (2013) pmid: 23526491
109. Rekhtman N, et al. Mod. Pathol. (2013) pmid: 23619604
110. Ragusa M, et al. Am. J. Clin. Oncol. (2014) pmid: 23357969
111. Kim ST, et al. Med. Oncol. (2013) pmid: 23307237
112. Russell PA, et al. J Thorac Oncol (2013) pmid: 23486266
113. Stella GM, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 23644698
114. Cai G, et al. Cancer Cytopathol (2013) pmid: 23495083
115. Yip PY, et al. J Thorac Oncol (2013) pmid: 23392229
116. Tochigi N, et al. Am. J. Clin. Pathol. (2011) pmid: 21502435
117. Shu C, et al. Mod. Pathol. (2013) pmid: 22996376
118. Wang R, et al. J Thorac Oncol (2014) pmid: 24481316
119. Karlsson A, et al. Oncotarget (2015) pmid: 26124082
120. Scoccianti C, et al. Eur. Respir. J. (2012) pmid: 22267755
121. Curr Opin Oncol (2014) pmid: 24463346
122. Ghimessy AK, et al. Cancers (Basel) (2019) pmid: 31600989
123. Chaft JE, et al. J Thorac Oncol (2013) pmid: 23857398
124. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
125. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
126. Kahn S, et al. Anticancer Res. () pmid: 3310850
127. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
128. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
129. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
130. Sci. STKE (2004) pmid: 15367757
131. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
132. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
133. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
134. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
135. Kim E, et al. Cancer Discov (2016) pmid: 27147599
136. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
137. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
138. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
139. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
140. Scheffzek K, et al. Science (1997) pmid: 9219684
141. Scholl C, et al. Cell (2009) pmid: 19490892
142. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
143. Tyner JW, et al. Blood (2009) pmid: 19075190
144. Valencia A, et al. Biochemistry (1991) pmid: 2029511
145. White Y, et al. Nat Commun (2016) pmid: 26854029
146. Wiest JS, et al. Oncogene (1994) pmid: 8058307
147. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
148. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
149. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033