FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Li Yu	Brain glioblastoma (GBM)	14 Nov 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1491954-01

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 Brain glioblastoma (GBM)
NAME Chen, Li Yu
DATE OF BIRTH 25 April 1973
SEX Female
MEDICAL RECORD # 48984710

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-39917A (PF22124)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 04 October 2022
SPECIMEN RECEIVED 04 November 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

ROS1 KATNA1-ROS1 fusion
KRAS G12V, amplification
BRAF D594N
CDKN2A/B CDKN2B loss, CDKN2A loss
GATA3 Q297fs*7
TERT promoter -124C>T
TP53 L111_H115del

3 Disease relevant genes with no reportable alterations: ***EGFR, IDH1, PDGFRA***

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TERT* promoter -124C>T** (p. 8)
- Targeted therapies with potential clinical benefit **approved in this patient's tumor type: Entrectinib** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT* promoter -124C>T** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 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)**
***ROS1* -** KATNA1-ROS1 fusion	Entrectinib	Ceritinib
		Crizotinib
7 Trials see p. 15		Lorlatinib
***KRAS* -** G12V, amplification	none	none
10 Trials see p. 13		

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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.

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

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

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[10]. 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[10-12]. 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[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
4 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[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[16,26-30].

GENE
ROS1

ALTERATION
KATNA1-ROS1 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The ROS1 TKIs crizotinib[47], entrectinib[48], ceritinib[49], and lorlatinib[50-51] have shown significant clinical activity for patients with ROS1-rearranged non-small cell lung cancer (NSCLC). Treatment with brigatinib[52], repotrectinib[53], cabozantinib[54-57], or taletrectinib[58-59] has resulted in clinical benefit for patients with ROS1-rearranged NSCLC that developed resistance to crizotinib or ceritinib. The Phase 1/2 TRIDENT-1 study of repotrectinib reported ORRs of 91% (10/11; Phase 1) and 86% (6/7; Phase 2) for patients who are tyrosine kinase inhibitor (TKI) naive with ROS1-rearranged non-small cell lung cancer (NSCLC); for patients who are TKI pretreated, the ORRs were 28% (5/18; Phase 1) and 50% (11/22; Phase 2)[60-61] . The Phase 2 TRUST study of taletrectinib reported ORRs of 87% (13/15) and 60% (3/5) for patients who are crizotinib naive and patients who have been pretreated with crizotinib with ROS1-rearranged NSCLC, respectively[62]. Two Phase 1 studies reported ORRs of 58% (7/12) and 33% (2/6) for patients with ROS1-rearranged NSCLC, respectively[58-59]. It is unclear if the rearrangement seen here results in expression of an oncogenic protein. Depending on the clinical context, alternative testing to confirm the presence of an oncogenic fusion at the RNA, protein, or DNA level should therefore be considered for treatment decisions.

FREQUENCY & PROGNOSIS

One study of 100 low-grade (Grade 2) and 168 high-grade (Grades 3-4) glioma samples failed to identify any GOPC-ROS1 fusions[63] while another study of 282 glioma samples identified only 1 GOPC-ROS1 fusion[33]. In an analysis of the TCGA dataset, ROS1 fusion was observed in one of 157 glioblastoma multiforme cases[64]. Case studies have also reported ROS1 fusions in glioblastoma[65-68]. Oncogenic fusions in receptor tyrosine kinases, including ALK, NTRK1/2/3, ROS1, and MET, are characteristic of a subset of infantile hemispheric high-grade gliomas with intermediate to good prognosis[69-70]. Published data investigating the prognostic implications of ROS1 alterations in glioblastoma are limited (PubMed, Dec 2021).

FINDING SUMMARY

The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[71]. ROS1 fusions involving a 5' partner joined with the 3' kinase domain (exons 36-42) of ROS1 have been characterized as activating and oncogenic[71-80] and clinically sensitive to ROS1-targeted therapies[48,51,81-83]. One or more of the rearrangements observed here were detected as a reciprocal fusion, are not clearly in-frame, or lack a fusion partner with an oligomerization domain or subcellular localization that may promote fusion protein activation[84], and it is unclear whether such events would lead to a production of an oncogenic variant.

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GENE
KRAS

ALTERATION
G12V, amplification

TRANSCRIPT ID
NM_004985.3

CODING SEQUENCE EFFECT
35G>T

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
76.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[85-90]. Clinical evidence that KRAS amplification in the absence of a concurrent KRAS activating mutation is sensitive to MEK inhibitors is limited. A Phase 2 study of selumetinib plus docetaxel in patients with gastric cancer reported 1/2 patients with KRAS amplification experienced a PR[91]. A patient with cervical cancer harboring both KRAS and PIK3CA amplification treated with the combination of trametinib and the AKT inhibitor GSK2141795 achieved a SD[92]. 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[93]. 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[94-95] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[96-97]. 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[98]. 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[99]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[100-101]. 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[102-103] . While clinical responses have been reported for patients with KRAS-mutated ovarian[104-107], cervical small cell neuroendocrine[108], or uterine cancer[106] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[109-112], pancreatic cancer[113-115], and NSCLC[110,116-117]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[92]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[118-120] and KRAS-mutated endometrioid adenocarcinoma[121].

FREQUENCY & PROGNOSIS

In the TCGA dataset, KRAS mutations or amplification was detected in 1.8% of glioblastomas (GBM)[122] and 2.8% of lower grade gliomas[123]. In other studies KRAS mutations were observed in 2 out of 125 pilocytic astrocytomas, 1 out 25 grade 1 and 2 astrocytomas[124-125], and 2 out of 94 patients with GBM[126]. While the importance of RAS signaling in astrocytomas has been established, there is very little information regarding clinical implications of KRAS alterations in human astrocytoma[124,127]. In mouse models of cancer, activating KRAS mutation in combination with AKT mutation was sufficient to induce GBM in astrocytes and neural progenitors[128]. Furthermore, mutant KRAS-driven signaling was required for the maintenance of mouse GBM tumors[129], suggesting that targeting KRAS signaling may be an appropriate therapeutic strategy in KRAS-driven GBMs.

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[86,130]. 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, E63K, R68S, and K117N have been characterized as activating and oncogenic[86,131-153]. In numerous cancer type-specific studies as well as a large-scale pan-cancer analysis, KRAS amplification was shown to correlate with increased expression[154-157]. Additionally, KRAS amplification correlated with sensitivity of cancer cell lines to KRAS knockdown, suggesting that amplified KRAS is an oncogenic driver[157].

POTENTIAL DIAGNOSTIC IMPLICATIONS

In pediatric gliomas lacking typical BRAF and NF1 driver alterations, RAS/MAPK hyperactivation arising from non-KIAA1549 fusions with BRAF, non-V600 BRAF mutations, FGFR1/2 fusions, FGFR1 mutations, RAF1 fusions, KRAS mutations, or MYB or MYBL1 rearrangements are typical of the WHO entity diffuse low-grade glioma, MAPK pathway-altered[158-161].

GENE
BRAF

ALTERATION
D594N

TRANSCRIPT ID
NM_004333.4

CODING SEQUENCE EFFECT
1780G>A

VARIANT CHROMOSOMAL POSITION
chr7:140453155

VARIANT ALLELE FREQUENCY (% VAF)
7.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical outcomes for patients with activating BRAF alterations treated with BRAF and MEK inhibitors are most extensive at the V600 codon; outcomes are more limited for BRAF class 3 kinase-impaired or inactivating mutations such as one or more of the alterations seen here. A retrospective study of immunotherapies in NSCLC reported a 78% DCR (7/9) for patients with BRAF class 3 mutations[162]. MEK inhibitors alone or in combination with BRAF inhibitors may be efficacious in these alterations; a basket trial of single-agent MEK inhibitor trametinib reported 1 PR, 8 SDs, and 9 PDs for these patients[163], and combination therapies reported individual responses in other basket trials[164-165]. A retrospective analysis in BRAF-mutated melanoma reported PD as the best response in BRAF class 3 alterations for 2 patients treated with MEK inhibitors and 3 patients treated with RAF inhibitors[166]. Single-agent BRAF inhibitor vemurafenib was not effective in a Phase 2 trial in NSCLC, which reported no responses for 6 patients with class 3 BRAF alterations[167]; a basket trial of vemurafenib also observed no responses for these patients (n=3)[168]. Investigational BRAF[169] and ERK[170] inhibitors are also in development; a basket trial of ulixertinib reported no responses and 3 SDs for patients across class 3-mutated tumors[170].

FREQUENCY & PROGNOSIS

Various studies have implicated BRAF alterations, including V600E and rearrangements, in the oncogenesis of pediatric low grade astrocytomas, including gangliogliomas[171-180]. BRAF alterations have been reported in 1-3% of gliomas including low grade gliomas[40,123,126,178,181-182] and glioblastomas (GBM)[122]. Studies have reported conflicting results as to whether BRAF mutations, including V600E, are more likely to be found in lower grade astrocytomas or higher grade glioblastomas[178,181,183], and the frequency of the BRAF V600E mutation in astrocytoma reported in the literature varies by cohort[184-186]. BRAF V600E is not strongly associated with prognosis in patients with astrocytoma[184,186]. While one study associated KIAA1549-BRAF fusion with improved prognosis in pediatric patients with low grade astrocytomas[187], others reported no significant association between BRAF rearrangements and outcome[188-191].

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[192-193]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[194-195]. Alterations such as the class 3 mutation seen here have been shown to require concomitant upstream RAS activity in contrast with independently activating BRAF V600 or class 2 alterations[196-208], and may activate the MEK-ERK signaling pathway via CRAF[196-198,205,209].

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[210-213]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[214] and palbociclib treatment[215-216]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[217-223]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[224-225], the clinical relevance of p14ARF as a predictive biomarker is not clear. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[218,220-221,226-228].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[229] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[122] than in those with lower grade gliomas (6%)[230]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[231-233]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[234]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[235]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[236]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[232,237]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[238-239].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[240-241]. 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[242-243]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[244-245]. One or more alterations observed here are predicted to result in p16INK4a loss of function[246-267]. One or more alterations seen here are predicted to result in p14ARF loss of function[250,267-270]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[271].

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[272]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[273-274]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[275-277]. 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[278-280]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
GATA3

ALTERATION
Q297fs*7

TRANSCRIPT ID
NM_001002295.1

CODING SEQUENCE EFFECT
889_890insC

VARIANT CHROMOSOMAL POSITION
chr10:8106065

VARIANT ALLELE FREQUENCY (% VAF)
24.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with hormone receptor-positive (HR-positive), HER2-negative metastatic breast cancer treated with selective estrogen receptor degraders alone or combined with CDK4/6 inhibitors, GATA3 mutations, as detected in liquid biopsies, have been associated with significantly shorter PFS (4.1 vs. 6.7 months, HR=2.4) and OS (14.1 vs. 27.1 months, HR=2.5) compared with GATA3 wild-type status in multivariate analyses, thereby suggesting that GATA3 mutations may predict worse outcomes on selective estrogen receptor degraders[281]. In early HR-positive breast cancer, however, GATA3 mutations have been linked with response to neoadjuvant aromatase inhibitors[282].

FREQUENCY & PROGNOSIS

Somatic mutations of GATA3 are most common in breast cancer (4-15%)[283-287] and occur infrequently in other solid tumor types, including cutaneous melanoma (2-6%)[288-290], gastric cancer (0-6%)[291-294], and lung cancer (1-3%)[295-297]. GATA3 mutations and protein expression in breast cancer are significantly associated with hormone receptor-positive (HR+) status[287,298-301]. The prognostic relevance of GATA3 alterations in breast cancer remains unclear, with some studies correlating GATA3 mutations or high GATA3 expression positively with improved OS[298,300-303], whereas other studies indicate no correlation between GATA3 alterations and outcomes[287,304].

FINDING SUMMARY

GATA3 encodes a zinc-finger transcription factor involved in a range of developmental pathways. Along with GATA2, it participates in control of adipocyte differentiation[305], and through control of cytokine expression it acts along with TBET as a master regulator of T-cell Th1/Th2 lineage determination[306]. Germline inactivating mutations in GATA3 result in a developmental disorder characterized by hypoparathyroidism, sensorineural deafness, and renal insufficiency (HDRS)[307]. GATA3 has been hypothesized to be required for BRCA1-mediated repression of proliferation-associated genes in breast tissue and in triple-negative breast tumors[308].

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253.2

CODING SEQUENCE EFFECT
-124C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295228

VARIANT ALLELE FREQUENCY (% VAF)
19.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[309]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[310]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[311].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[312-313], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[312-316]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[312,314]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[235]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[317]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[312,314,317-318]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v1.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[319]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[320-322]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[323-325], as well as tandem mutations at positions −124/−125 bp and −138/−139 bp[323].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2022)[326]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v1.2022)[327].

GENE
TP53

ALTERATION
L111_H115del

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
331_345delCTGGGCTTCTTGCAT

VARIANT CHROMOSOMAL POSITION
chr17:7579341-7579356

VARIANT ALLELE FREQUENCY (% VAF)
23.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[328-331] or p53 gene therapy such as SGT53[332-336]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[337]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[338]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[339]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[118]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[340]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[341]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[342]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[336]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[343]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[344].

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[345-346]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[235]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[347-352]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[353]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[235]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[354].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[355]. Alterations such as seen here may disrupt TP53 function or expression[356-360].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[361-363], including sarcomas[364-365]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[366] to 1:20,000[365]. 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[367]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[368-373]. 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[368-369]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[374]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[372,375-376]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Entrectinib

Assay findings association

ROS1
KATNA1-ROS1 fusion

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is FDA approved to treat adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients with NTRK fusion-positive solid tumors that lack a known acquired resistance mutation and are metastatic or likely to result in severe morbidity after surgical resection, have no satisfactory alternative treatments, or have progressed following treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[48,377-379] and clinical benefit in other solid tumor types[380-383] , ROS1 fusions may predict sensitivity to entrectinib. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, alternative testing for the presence of an oncogenic fusion may be appropriate to determine whether this therapeutic approach would be relevant.

SUPPORTING DATA

Integrated analysis of the ALKA-372-001, STARTRK-1, and STARTRK-2 trials evaluating entrectinib for TKI-naive patients with ROS1 fusion-positive non-small cell lung cancer (NSCLC) reported an ORR of 68%, median PFS of 15.7 months, and median OS of 47.8 months; among patients with measurable baseline central nervous system metastases, an intracranial ORR of 80% (20/25) and median intracranial PFS of 8.8 months was achieved[384]. Clinical benefit has also been reported for other ROS1 fusion-positive solid tumors, including PRs for 3/3 pediatric patients with glioma or inflammatory myofibroblastic tumors[385], a PR for an adult patient with acral lentiginous melanoma[48,382] , a PR for a patient with metastatic papillary thyroid cancer[386], and SD for an adult patient with metastatic pancreatic cancer[387]. In a Phase 1/1b trial for pediatric or adolescent patients, entrectinib elicited 4 CRs and 2 PRs in 8 evaluable patients with primary CNS tumors, all of whom harbored either NTRK or ROS1 fusion[388]. Two patients with CNS tumors containing either a ROS1-ARCN1 fusion or an ETV6-NTRK3 fusion experienced initial clinical benefit after treatment with entrectinib monotherapy[389-390] . One patient with an EML4-NTRK3 fusion-positive CNS tumor experienced limited clinical benefit with entrectinib monotherapy[389]. Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without central nervous system (CNS) metastases and with NTRK, ROS1, or ALK fusions[48,377-380,391] , and preclinical sensitivity has been observed in NTRK fusion-positive acute myeloid leukemia (AML) cell lines[392]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutated neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received a prior ALK tyrosine kinase inhibitor (TKI) or crizotinib, respectively[48].

Ceritinib

Assay findings association

ROS1
KATNA1-ROS1 fusion

AREAS OF THERAPEUTIC USE

Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is FDA approved to treat metastatic non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements, as detected by an FDA-approved test. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of Phase 2 clinical studies demonstrating benefit to patients with ROS1-rearranged NSCLC[49,393], ROS1 rearrangements may predict sensitivity to ceritinib. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, alternative testing for the presence of an oncogenic fusion may be appropriate to determine whether this therapeutic approach would be relevant.

SUPPORTING DATA

In a Phase 2 basket trial of ceritinib which enrolled patients with ALK-rearranged glioblastoma, the ORR was 0% (0/12)[394]. An infant with ALK fusion-positive glioblastoma and progression on temozolomide experienced stable residual disease for nearly two years with ceritinib treatment[69]. However, ceritinib did not elicit disease control in any of 12 adults with ALK-positive GBM in a Phase 2 study[394]. Ceritinib has been primarily investigated for the treatment of ALK-rearranged NSCLC. A Phase 3 study of ceritinib for ALK inhibitor-naive patients with ALK-rearranged NSCLC observed a whole-body (WB) ORR of 63.7%, a WB DCR of 89.5%, and PFS of 11.1 months[395]. Following progression on prior chemotherapy and crizotinib, patients with ALK-rearranged NSCLC achieved a WB ORR of 38.6%, WB DCR of 77.1%, and PFS of 5.4 months on ceritinib[396]. A Phase 1 study of ceritinib reported a 58% response rate for 114 patients with ALK-rearranged NSCLC and a response rate of 56% for 80 of these patients who had previously been treated with crizotinib[397]. A Phase 1 trial of combination ceritinib and chemotherapy for patients with advanced solid tumors reported a 20% (3/15) ORR, median PFS of 4.8 months, and a median OS of 10.2 months; clinical responses were observed for patients with head and neck carcinoma, unknown primary carcinoma, and cholangiocarcinoma[398]. A patient with colorectal carcinoma and a STRN-ALK fusion exhibited clinical benefit from ceritinib[399]. A patient with pancreatic ductal adenocarcinoma harboring an EML4-ALK fusion was reported to have a response lasting 2 months, but developed resistance within 7 months[400].

Crizotinib

Assay findings association

ROS1
KATNA1-ROS1 fusion

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Crizotinib has shown clinical and preclinical evidence of activity in ROS1-rearranged NSCLC[47,77,80,82-83,401-407] and IMT[79]. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, alternative testing for the presence of an oncogenic fusion may be appropriate to determine whether this therapeutic approach would be relevant.

SUPPORTING DATA

A Phase 1 study of crizotinib combined with temozolomide and radiotherapy reported a median PFS of 16.8 months and a median OS of 31.4 months for patients with glioblastoma[408]. A Phase 1 study of crizotinib in pediatric patients with solid tumors or lymphoma reported intratumoral hemorrhage in 2 patients with primary central nervous system (CNS) tumors, and patients with CNS lesions were subsequently excluded from the study[409].

Lorlatinib

Assay findings association

ROS1
KATNA1-ROS1 fusion

AREAS OF THERAPEUTIC USE

Lorlatinib is a tyrosine kinase inhibitor that targets ALK and ROS1. It is FDA approved to treat patients with ALK-positive non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[50-51,410-413] and preclinical[413-415] evidence, ROS1 activation may predict sensitivity to lorlatinib. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, alternative testing for the presence of an oncogenic fusion may be appropriate to determine whether this therapeutic approach would be relevant.

SUPPORTING DATA

Clinical data on the efficacy of lorlatinib to treat glioma or glioblastoma are limited (PubMed, Mar 2022). A pediatric patient with glioma harboring an ALK fusion benefited from treatment with lorlatinib, with disease recurrence at 6 months after the first treatment cycle and re-treatment eliciting a near complete response[416]. Lorlatinib has primarily been investigated for ALK- and ROS1-positive NSCLC as an approach to overcome resistance to prior TKIs[50,417] . A Phase 1 study evaluating lorlatinib for the treatment of NSCLC reported an ORR of 50% (6/12) and a median duration of response (mDOR) of 12 months for ROS1-positive patients[50]. The subsequent Phase 2 study reported an ORR of 61.5% (8/13) for the crizotinib-naive and 26.5% (9/34) for the crizotinib-treated ROS1-positive population, and 3/6 crizotinib-naive and 8/19 of crizotinib-pretreated patients with brain metastasis achieved CR[410]. Lorlatinib also showed clinical activity for 2 patients with NSCLC and EZR-ROS1 fusion whose tumors did[413] or did not[411] additionally harbor ROS1 S1986Y/F dual mutations. Preclinical studies in murine models support the sensitivity of ROS1-rearranged glioblastomas to lorlatinib[414-415] .

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

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

GENE

KRAS

ALTERATION

G12V, amplification

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.

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado, Toronto (Canada), Indiana

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03284502

PHASE 1

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

TARGETS
MEK, RAFs, NRAS

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

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)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT04214418

PHASE 1/2

Study of Combination Therapy With the MEK Inhibitor, Cobimetinib, Immune Checkpoint Blockade, Atezolizumab, and the AUTOphagy Inhibitor, Hydroxychloroquine in KRAS-mutated Advanced Malignancies

TARGETS PD-L1, MEK

LOCATIONS: Rhode Island, New York

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

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04892017

PHASE 1/2

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

TARGETS ULK1, ULK2, MEK

LOCATIONS: Massachusetts, Texas, Pennsylvania

GENE
ROS1

ALTERATION
KATNA1-ROS1 fusion

RATIONALE
Activating ROS1 fusions may predict sensitivity to inhibitors of ROS1. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, alternative testing for the presence of an oncogenic fusion may be appropriate to determine whether these therapeutic approaches would be relevant.

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
TRKA, ALK, ROS1, TRKB, TRKC

LOCATIONS: Taipei (Taiwan), Fuzhou (China), Fujian (China), Tainan (Taiwan), Zhejiang (China), Hangzhou (China), Zhanggong (China), Shanghai (China), Sha Tin (Hong Kong), Kowloon (Hong Kong)

NCT04589845

PHASE 2

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

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

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

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA

LOCATIONS: Zhejiang (China), Shanghai City (China), Shanghai (China), Guangzhou (China), Wuhan City (China), Tianjin (China), Beijing (China), Chengdu (China), Harbin (China)

NCT05097599

PHASE 2

Strata PATH™ (Precision Indications for Approved Therapies)

TARGETS
ERBB2, ROS1, ALK, BRAF, MEK, PARP

LOCATIONS: Ohio

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT04693468

PHASE 1

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

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

LOCATIONS: Texas

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

ALK
V163L

CUL4A
R525C

DAXX
E457del

MERTK
P481S

MET
M822I

MLL2
A1791V

PDCD1 (PD-1)
V11I

PTEN
H61Y

SMARCA4
G19C

SMO
R671W

SPEN
T796S

STK11
F354L

WHSC1 (MMSET)
S389F

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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 fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.3.0

The median exon coverage for this sample is 894x

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