FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Soft tissue sarcoma (NOS)

REPORT DATE

TRF#

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

PATIENT

DISEASE Soft tissue sarcoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - TMB-High (40 Muts/Mb)

Genomic Findings

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

NTRK1 A107V - subclonal, rearrangement intron 6†
CD274 (PD-L1) amplification
EGFR amplification - equivocal†
PDCD1LG2 (PD-L2) amplification
ATRX T1582fs*24
CAD V1226I
CDKN2A/B loss
CTNNA1 R551Q
EPHA3 amplification
FANCD2 truncation intron 31
FOXP1 G433*, amplification
JAK2 amplification - equivocal†
KDM4C amplification
MITF amplification
NOTCH1 D1870N
PAX5 loss
PCLO A915S - subclonal†
PRKDC T1269M
PTPN11 V428M
SMARCA4 G1232D
TP53 R273H, R175H
ZMYM3 rearrangement exon 17

† See About the Test in appendix for details.

15 Therapies with Clinical Benefit
0 Therapies with Lack of Response
24 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Pembrolizumab	Atezolizumab
		Avelumab
		Cemiplimab-rwlc
		Durvalumab
		Nivolumab
10 Trials *see p. 27*		
Tumor Mutational Burden - TMB-High (40 Muts/Mb)	none	Atezolizumab
		Avelumab
		Cemiplimab-rwlc
		Durvalumab
		Nivolumab
10 Trials *see p. 29*		Pembrolizumab

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
NTRK1 **-** A107V - subclonal, rearrangement intron 6	Larotrectinib	Crizotinib
7 Trials *see p. 34*		
CD274 (PD-L1) **-** amplification	none	Atezolizumab
		Avelumab
		Cemiplimab-rwlc
		Durvalumab
		Nivolumab
10 Trials *see p. 31*		Pembrolizumab
EGFR **-** amplification - equivocal	none	Afatinib
		Cetuximab
		Dacomitinib
		Erlotinib
		Gefitinib
		Lapatinib
6 Trials *see p. 33*		Panitumumab
PDCD1LG2 (PD-L2) **-** amplification	none	Atezolizumab
		Avelumab
		Cemiplimab-rwlc
		Durvalumab
		Nivolumab
10 Trials *see p. 36*		Pembrolizumab

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

BIOMARKER
Microsatellite status

CATEGORY
MSI-High

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden [1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[3-4] [2,5-6], including the approved therapies nivolumab[7-8], pembrolizumab [9-10], atezolizumab, avelumab, and durvalumab[3-4] [5].

FREQUENCY & PROGNOSIS

Reports of MSI in sarcomas in the literature are conflicting and varied due to substantial heterogeneity, lack of consensus on the markers and methods used for MSI assessment, and small sample size in most studies [11]. In a computational analysis of paired tumor and normal sarcomas in the TCGA dataset, of which 40% were leiomyosarcomas and 25% were liposarcomas, only 0.8% (2/255) of samples were MSI-high (MSI-H) [12]. In smaller studies of soft tissue sarcoma, reports of MSI at any level have been rare, with the highest incidences between 11% (2/18) to 25% (10/40) of cases [13-18]. In one study, MSI was reported to occur more frequently in high-grade soft tissue sarcomas compared with lower grade [19]. However, the prognostic significance of MSI in sarcoma is unknown (PubMed, Jan 2018).

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 [20]. 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 [20-22]. This sample has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in >30% of microsatellite markers [23-25]. MSI-H status indicates high-level deficiency in MMR and typically correlates with loss of expression of at least one, and often two, MMR family proteins [20,22,24-25]. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes [20], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) [26]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers [26-28] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000 [29-31]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER
Tumor Mutational Burden

CATEGORY
TMB-High (40 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4 [32], anti-PD-L1 [33-36], and anti-PD-1 therapies [9-10,37]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) for patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[10]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbored elevated mutational burden reported higher overall response rates to pembrolizumab [9-10,37]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses (PRs) following treatment with pembrolizumab [38] or nivolumab [39], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab [40], 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab [41], and 2 patients with microsatellite-stable rectal cancers, 1 who achieved an ongoing PR to pembrolizumab and the other an ongoing complete response to nivolumab [42]. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab [32,43] and anti-PD-1/anti-PD-L1 treatments [34]. For patients with metastatic urothelial carcinoma (mUC), those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations [muts] per megabase [Mb]) compared to nonresponders (6.4 muts/Mb)[33], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival [35]. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors), a TMB of ≥16 muts/Mb associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone[44].

FREQUENCY & PROGNOSIS

Soft tissue sarcomas harbor a median TMB of 2.5 mutations per megabase (muts/Mb), with angiosarcoma (13.4%) and malignant peripheral nerve sheath tumor (MPNST) (8.2%) having the highest percentage of cases with high TMB (>20 muts/Mb)[45]. Increased mutation burden has been reported in undifferentiated pleomorphic sarcomas as compared to Ewing sarcomas or rhabdomyosarcomas [46-48]. The association of mutational burden and prognosis of specific soft tissue sarcoma subtypes has not been extensively investigated in the literature (PubMed, Dec 2018).

FINDING SUMMARY

Tumor mutational 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 [49-50] and cigarette smoke in lung cancer [10,51], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes [52-56], and microsatellite instability (MSI) [52,55-56]. This sample harbors a high TMB. This type of mutation load has been shown to be associated with sensitivity to immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma [32], anti-PD-L1 therapy in urothelial carcinoma [33], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer [9-10], potentially due to expression of immune-reactive neoantigens in these tumors [10].

GENE
NTRK1

ALTERATION
A107V - subclonal, rearrangement intron 6

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data indicate that NTRK1 fusions predict sensitivity to TRK inhibitors [57-66] such as larotrectinib, entrectinib, AZD7451, belizatinib, PLX7486, and to the mutikinase inhibitors crizotinib and lestaurtinib. Larotrectinib is approved to treat patients with NTRK fusion-positive solid tumors based on significant clinical efficacy in that population. Analysis of combined data from several larotrectinib studies reported an ORR of 81% (88/109) in adult and pediatric patients with various solid tumors harboring NTRK fusions treated with larotrectinib; the responses were durable and CR was observed in 17% of patients [65]. Pooled analysis of 3 Phase 1/2 trials of entrectinib for adult patients with NTRK fusion-positive solid tumors reported an ORR of 57% (31/54), median PFS of 11.2 months, and median OS of 20.9 months[67]. Similar activity was observed for patients with NTRK1 fusions [ORR of 59% (13/22)] or patients with CNS metastasis [ORR of 55% (6/11)][67]. Acquired resistance to larotrectinib and entrectinib due to the emergence of kinase domain mutations in NTRK fusions has been reported in some patients [64-65,68-69]. Next-generation TRK inhibitors in development, such as LOXO-195 and repotrectinib, have shown preclinical and clinical activity against acquired NTRK resistance mutations [68,70]. Patients with NTRK1 fusions have also experienced clinical benefit from crizotinib, including a durable near CR [60] and a partial remission of lung masses [61] in patients with infantile fibrosarcoma harboring LMNA-NTRK1 fusions and a minor radiographic response in a patient with lung adenocarcinoma and an MPRIP-NTRK1 fusion [57]. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, it is not known whether these therapeutic approaches would be relevant. It is also not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

NTRK1 fusions have been detected in multiple types of sarcomas including infantile fibrosarcoma [58,66,71]. In the Sarcoma MSKCC/Broad dataset, putative high-level amplification of NTRK1 has been reported in 4.8% of tumors [72]. NTRK1 mutations are rare in sarcomas, occurring in <1% of the samples analyzed in COSMIC (Dec 2018). TRKA expression has been demonstrated in some sarcoma subtypes such as osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma [73-75]. In a preclinical study, overexpression of TRKA induced cell death in sarcoma and neuronal cancer cell lines [76]. Published data investigating the prognostic implications of NTRK1 alterations in sarcoma are limited (PubMed, Dec 2018). Two patients with infantile fibrosarcoma harboring LMNA-NTRK1 fusion experienced a CR [60] or PR [61] in response to crizotinib.

FINDING SUMMARY

NTRK1 encodes the receptor tyrosine kinase TRKA, which plays a role in the development of the nervous system by regulating cell proliferation, differentiation, and survival of neurons. TRKA is activated upon binding of its ligand NGF to promote several downstream signaling pathways including GRB2-RAS-MAPK, NF-Kappa-B, and RAS-PI3K-AKT1 [77-80]. NTRK1 fusions that include an N-terminal oligomerization-promoting partner gene linked to the kinase domain of TRKA (aa 510-781) have been characterized as activating, exhibiting constitutive kinase activity and tyrosine phosphorylation [57-58,81-86]. Certain NTRK1 rearrangements affecting the extracellular domain have also been shown to be activating and transforming [80,87-89]. NTRK1 rearrangements such as observed here that are detected as a reciprocal fusion, are not clearly in-frame, or may lack a fusion partner may be indicative of an activating rearrangement event, such as a fusion; however, it is unclear whether an oncogenic rearrangement is present and expressed in this case. Patients with NTRK1 fusions have experienced clinical benefit from crizotinib [57,60-61] and from TRK inhibitors, including LOXO-101 [58] and entrectinib [62,90]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

On the basis of strong clinical evidence, CD274 amplification and PD-L1 overexpression may predict sensitivity to antibodies targeting PD-L1 or PD-1. Patients with high tumor PD-L1 expression across multiple solid tumor types have exhibited improved overall survival (OS) with the FDA-approved PD-L1 antibody atezolizumab[91-93]. Compared with PD-L1-negative patients, clinical studies with the PD-L1 antibody durvalumab have suggested higher response rates for patients with urothelial carcinoma and PD-L1-positive tumor or immune cells[94-95], non-small cell lung cancer and PD-L1-positive tumor cells[96-97], or head and neck squamous cell carcinoma and PD-L1-positive tumor cells[98-99]. The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses [100], including in patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[101-102]. Clinical studies have reported that PD-L1 amplification [100] or expression[103-104] in solid tumors is associated with response to anti-PD-1 antibodies. However, a study evaluating nivolumab in patients with urothelial carcinoma observed no correlation between OS benefit and PD-L1 expression levels[105]. JAK2 has been reported as important for PD-L1 expression in Hodgkin lymphoma and primary mediastinal B-cell lymphoma cell lines, and JAK2 inhibition has been reported to decrease PD-L1 transcript accumulation [106-107]. Therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for a patient with PD-L1 amplification.

FREQUENCY & PROGNOSIS

Amplification of CD274 has been observed in 1.4% of sarcomas [72]. PD-L1 protein expression was observed in 50% of all sarcoma cases in one study [108], although in another study, differences in PD-L1 expression were observed between the tumor (12%), lymphocytes (30%), and macrophages (58%) within sarcomas [109]. Overexpression of PD-L1 has been shown to correlate with poor prognosis in malignant melanoma, colon, hepatocellular, renal cell, and ovarian carcinomas [110-114], although data regarding the prognostic significance of PD-L1 expression in soft tissue sarcomas is conflicting [109,115].

FINDING SUMMARY

CD274 encodes the programmed cell death ligand 1 (PD-L1), also known as B7-H1, which is a cell surface molecule important for regulating the activity of T-cells through binding to various T-cell receptors. Although PD-L1 is a costimulatory molecule for naive T-cells, it can provide inhibitory signals to activated T-cells through interactions with the receptors PD-1 or CD80 [116-117]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells [118-120]. PD-L1 amplification has been reported to be associated with increased expression [102,106,121-122].

GENE
EGFR

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors, including erlotinib, gefitinib, afatinib, dacomitinib, lapatinib, osimertinib, cetuximab, and panitumumab [123-128]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin [129-130] that has also shown benefit in patients with CRC and melanoma [131-132]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy [133-136]. Preclinical studies have reported that EGFR-mutant cells [133-135], including cells with exon 20 insertions [137], are sensitive to HSP90 inhibitors. The reovirus Reolysin targets cells with activated RAS signaling [138-140] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer [141-149].

FREQUENCY & PROGNOSIS

EGFR mutation and amplification have been observed in 1% and 4% of soft tissue sarcomas, respectively (COSMIC, Dec 2018)[72]. EGFR amplification has also been found in 26% of malignant peripheral nerve sheath tumors (MPNST)[150]. EGFR overexpression and/or activation has been reported in a number of sarcomas [151-155]. EGFR expression was associated with decreased probability of overall survival in a study of sarcomas, 42/281 of which were synovial sarcomas [156], whereas a subsequent study did not correlate EGFR overexpression with poor prognosis in synovial sarcoma specifically [151]. EGFR was found to be overexpressed in bone metastases of soft tissue sarcomas but was not associated with risk of primary tumor metastasis [157].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide [158]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types [159-161].