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

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.

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

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.

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].

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

PDCD1LG2 amplification, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-1, PD-L1, or PD-L2 antibodies. The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses in several cancer types, including melanoma, NSCLC, renal cell carcinoma [162-170], and Hodgkin lymphoma, which harbors frequent PD-L2 copy number gains[101-102]. The PD-L1 antibody atezolizumab does not block interaction between PD-1 and PD-L2; however, multiple clinical studies with atezolizumab have reported an association between increased PD-L2 expression and response or improved overall survival in multiple solid tumor types, thereby suggesting that PD-L2 overexpression may serve as a biomarker of response[92-93,171]. Additionally, JAK2 has been reported as important for PD-L2 expression in Hodgkin lymphoma and PMBCL cell lines, and JAK2 inhibition has been reported to decrease PD-L2 transcript accumulation in preclinical studies [106-107]. Therefore, JAK2 inhibitors may also be relevant for a patient with PD-L2 amplification. Ruxolitinib is a kinase inhibitor that targets JAK1 and JAK2 and is approved to treat intermediate or high-risk myelofibrosis [172].

FREQUENCY & PROGNOSIS

Amplification of PDCD1LG2 has been observed in 1% of sarcomas [72]. A case study of a patient with parapharyngeal liposarcoma observed PD-L2 expression on liposarcoma and endothelial cells [173]. Published data investigating the prognostic implications of PDCD1LG2 alterations in sarcomas are limited (PubMed, Dec 2018).

FINDING SUMMARY

PDCD1LG2 encodes the programmed cell death 1 ligand 2 (PD-L2), also known as CD273, PD-L2, and B7-DC, which is essential for T-cell proliferation and interferon production. PD-1 signaling, which can be stimulated by PD-L2, results in 'T-cell exhaustion', a temporary inhibition of activation and proliferation that can be reversed on removal of the PD-1 signal [116-117]. Amplification of PDCD1LG2 and the adjacent locus CD274, encoding PD-L1, has been reported in 29% of primary mediastinal B-cell lymphoma (PMBCL) cases, and PDCD1LG2 copy number gain has been reported to correlate with increased PD-L2 protein expression as determined by immunohistochemistry [174-175].

GENE
ATRX

ALTERATION
T1582fs*24

POTENTIAL TREATMENT STRATEGIES

No targeted therapies are available to address ATRX inactivation. Although ATR inhibition is being investigated as a potential therapeutic approach in the context of ALT, a preclinical study demonstrated that ATRX inactivation is not sufficient to confer sensitivity to ATR inhibitors [176]. However, ATRX-deficient GBM cells were sensitive to the double-strand break-inducing agents doxorubicin, irinotecan, and topotecan but not single-strand break-inducing agents such as temozolomide [177]. Preclinical evidence suggests that ATRX may be required for CDK4/6 inhibitors to be most effective [178].

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT [179]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[179-181], 12.6% of pheochromocytomas and paragangliomas [182], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[183-187]. ATRX loss in PNET[180,188] and melanoma [189] and mutation in other neuroendocrine tumors [182] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy [177]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma [190-193] and has been proposed as a distinguishing biomarker [191-193]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma [184-187]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation [191]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[194-195].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance [196-197]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[179,195,198-199]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function [200-202]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors [176,196]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[203].

GENE
CAD

ALTERATION
V1226I

POTENTIAL TREATMENT STRATEGIES

There are no therapies available to target alterations in CAD.

FREQUENCY & PROGNOSIS

Mutations in this gene have been observed in ~5% of Burkitt lymphomas in one study [204] and 1% of cancer samples in the COSMIC database (COSMIC, 2018).

FINDING SUMMARY

CAD encodes an enzyme involved in pyrimidine biosynthesis in the cell. CAD is activated by the mitogen-activated protein (MAP) kinase and is required for cell proliferation [205].

GENE
CDKN2A/B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib [206-209]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment [210-211], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[212-213 214-218]; 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 [219-220], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Putative homozygous deletion of CDKN2A and CDKN2B has been reported in 5% of sarcoma samples analyzed in the MSKCC dataset [72]. In some sarcomas, such as malignant peripheral nerve sheath tumor, rhabdomyosarcoma, and Ewing sarcoma, loss of p16INK4a has been reported at 50-83% [221-222]. The loss of CDKN2A and CDKN2B and/or the reduction of p15INK4b and p16INK4a protein levels has been noted in multiple types of sarcomas [221,223-226]. Loss of CDKN2A and/or the loss of p16INK4a expression has been associated with poor prognosis in patients with some types of sarcoma, including leiomyosarcoma, clear cell sarcoma, osteosarcoma, and malignant peripheral nerve sheath tumors [221,226-227].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b [228-229]. 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 [230-231]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition [232-233]. This alteration is predicted to result in p16INK4a [234-255] loss of function. This alteration is predicted to result in p14ARF [238,255-258] loss of function. The CDKN2B alteration is predicted to inactivate p15INK4b [259].

GENE
CTNNA1

ALTERATION
R551Q

POTENTIAL TREATMENT STRATEGIES
There are no available targeted therapies to address genomic alterations in CTNNA1. In two preclinical studies, treating CTNNA1-deficient cells either with the MAPK inhibitor PD98059 or the SMO inhibitor cyclopamine had significant effect on cell proliferation [260-261].

FREQUENCY & PROGNOSIS
CTNNA1 mutations have been observed with highest incidence in uterine corpus endometrial carcinoma (6.8%)[262], skin cutaneous melanoma (6.4%)[263], colorectal adenocarcinoma (4.4%)[262], and stomach adenocarcinoma (3.1%) TCGA datasets (cBioPortal, 2019). CTNNA1 mutations have been observed in patients with hereditary diffuse gastric carcinoma without CDH1 mutations [264-265]. Reduced CTNNA1 expression in patients with breast cancer has been correlated with a poor clinical outcome and breast cancer brain metastasis [266-267]. Deletion and hypermethylation of CTNNA1 has been observed in up to 22% (18/83) of myelodysplastic syndrome (MDS) cases and associated with poor clinicopathological features [268-270] and a trend for inferior survival [268]. Loss of CTNNA1 expression via 5q deletion or hypermethylation has been reported as a frequent event in acute myeloid leukemia and associated with shorter relapse-free survival in one study [270-272].

FINDING SUMMARY
CTNNA1 encodes alpha-catenin, a member of the cadherin family that functions in cell adhesion. Alpha-catenin acts as a tumor suppressor, through mechanisms that can vary by tissue [273-274]. Alpha-catenin is one of three catenin proteins that are in complex with E-cadherin to help mediate cell-cell adhesion in epithelial tumor suppression [273-274]; loss of cell adhesion may contribute to cancer cell invasiveness and formation of metastases. In epidermal cells, alpha-catenin acts as a tumor suppressor by inducing YAP1 phosphorylation and cytoplasmic localization [267,275]. Alpha-catenin also acts as a tumor suppressor by interacting with IKBalpha to influence the NF-KB pathway in E-cadherin-negative basal-like breast cancer cells [267]. Loss of alpha-catenin expression is also hypothesized to alter the balance between the cytoplasmic (cell adhesion) and nuclear (cell proliferation) functions of beta-catenin, further contributing to oncogenesis [276].

GENE
EPHA3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies that target EPH receptor mutation or amplification in cancer. A humanized monoclonal antibody targeting EPHA3 has exhibited several clinical responses and a tolerable safety profile in a Phase 1/2 trial in hematological malignancies[277-278], although EPHA3 amplification, expression, or mutations have not been evaluated as biomarkers for efficacy. Furthermore, clinical trials for this therapy are not recruiting.

FREQUENCY & PROGNOSIS
EPHA3 mutations have been reported in a range of tumor types, including lung adenocarcinoma (8–16%), melanoma (8–14%), diffuse large B-cell lymphoma (8%), gastric carcinoma (7%), and colorectal carcinoma (CRC; 5%)(cBioPortal, 2018) [279-282]. EPHA3 amplification has been reported most frequently in prostate adenocarcinoma (7%), sarcoma (5%), and lung squamous cell carcinoma (4%)(cBioPortal, 2018). EPHA3 mRNA has been reported to be highly expressed in glioma samples, as compared with normal brain tissue, and high EPHA3 mRNA expression has been found to be associated with an aggressive glioblastoma subtype [283]. EPHA3 expression has been correlated with poor prognosis in studies of gastric carcinoma, hepatocellular carcinoma, small cell lung cancer, and CRC [284-287]. EPHA3 expression has been observed in hematological malignancies, and low incidences of EPHA3 amplification and loss of heterozygosity have both been reported in leukemias and lymphomas [288-289]. Although EPHA3 expression is frequently associated with advanced disease, conflicting data have been reported [290].

FINDING SUMMARY
EPHA3 encodes a member of the EPH family of receptor tyrosine kinases, which have been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration [291-292]. EPHA3 has been reported to be amplified in cancer [293], and EPHA3 copy number has been shown to associate with gene expression levels [289]. Predominantly inactivating EPHA3 mutations have been reported in several cancers, and preclinical studies have found that mutations in EPHA3 may reduce activity through diverse mechanisms [294-300]. Conflicting data have been published regarding the tumor-promoting and tumor-suppressive activities of EPHA3 in cancer, which are likely context dependent [283,290,301].

GENE
FANCD2

ALTERATION
truncation intron 31

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies that directly address genomic alterations in FANCD2. However, somatic FANCD2 alterations may predict cancer sensitivity to DNA-damaging drugs, such as cisplatin or mitomycin C, and to PARP inhibitors [302-304]. The PARP inhibitors olaparib and rucaparib are FDA approved to treat patients with BRCA1/2-mutant ovarian cancer, and PARP inhibitors are in clinical trials in patients with solid tumors.

FREQUENCY & PROGNOSIS
Somatic mutations in FANCD2 are very infrequently observed (<1%) in human malignancies (COSMIC, 2017).

FINDING SUMMARY
FANCD2 encodes a key component of the Fanconi anemia (FA) DNA damage response system. The FA core complex (FANCA/B/C/E/F/G/L/M) is a nuclear E3 ubiquitin ligase, which is recruited to the sites of DNA damage/DNA repair [305]. The FA core complex then activates FANCD2 and FANCI via monoubiquitination, leading to their co-localization with FANCD1/BRCA2, BRCA1, RAD51, PCNA, and other proteins at the DNA repair foci on chromatin. The activity of this complex is essential for prevention of chromosome breakage caused by DNA damage [306]. Germline mutations in FANCD2 cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair [307].

GENE
FOXP1

ALTERATION
G433*, amplification

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies available to address alterations in FOXP1.

FREQUENCY & PROGNOSIS
Loss of FOXP1 expression has been reported to be a frequent event in endometrial cancer [308]. FOXP1 translocations have been described in acute lymphoblastic leukemia [309-310], and deletions of the chromosomal region where FOXP1 is located have been reported in acute myeloid leukemia and myeloproliferative neoplasms [311-312]. Genomic rearrangements that disrupt the 5' regulatory region of FOXP1 have been detected and characterized in several lymphomas [313-315]. Such alterations have been demonstrated to result in expression of N-terminally truncated variants of FOXP1, or aberrant expression of full length FOXP1 driven by strong regulatory elements, such as IGH, as observed in the t(3;14)(p13;q32) translocation [316]. In a genome-wide association study, polymorphisms at the FOXP1 locus were found to be significantly associated with Barrett esophagus and esophageal adenocarcinoma [317]. Conflicting data have been presented on the prognostic impact of FOXP1 expression, as high expression of FOXP1 is associated with poor prognosis in patients with cutaneous large B-cell lymphomas or mucosal tissue-associated lymphoid tissue (MALT) lymphomas, but improved prognosis in patients with breast or lung cancer [313-314,318-320].

FINDING SUMMARY
FOXP1 encodes the protein 'forkhead box protein P1', a transcription factor previously reported as a tumor suppressor, but one which can also function as an oncogene when shorter isoforms are expressed [321-322].

GENE
JAK2

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
On the basis of extensive clinical data in myelofibrosis, a disease type that frequently harbors the JAK2 V617F mutation [172,323-325], and a case report in chronic myelomonocytic leukemia[326], JAK2 activating mutations may predict sensitivity to JAK2 inhibitors, such as the approved agent ruxolitinib. Other alterations that activate JAK2, such as fusions [327-333] or amplification[334-335], may also confer sensitivity to JAK2 inhibitors, on the basis of clinical data in myeloid neoplasms as well as preclinical data. Preclinical studies have suggested that activating alterations in JAK2 may confer sensitivity to HDAC inhibitors [336-338] or HSP90 inhibitors [339-340].

FREQUENCY & PROGNOSIS
JAK2 amplification has been reported in 1-5% of sarcomas (cBioPortal, Jan 2019). Activation of a JAK family kinase substrate, STAT3, has been reported to occur in leiomyosarcoma and is associated with better prognosis [341].

FINDING SUMMARY
JAK2 encodes Janus kinase 2, a tyrosine kinase that regulates signals triggered by cytokines and growth factors [342]. JAK2 is often mutated in hematopoietic and lymphoid cancers. Cell lines and primary lymphoid cancer cells from a small number of patients with the JAK2 amplification exhibit overabundance of JAK2 mRNA, protein, and phosphorylated JAK2 targets and respond to JAK2 inhibitors such as ruxolitinib similarly to the JAK2-rearranged (activated) cell lines and primary blood cells from patients [106,331].

GENE
KDM4C

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
Small molecules that target the KDM4 proteins are in preclinical development [343], but no therapies are currently available to address mutations in KDM4C.

FREQUENCY & PROGNOSIS
KDM4C mutations are rare in cancer (COSMIC, 2018). Increased expression of KDM4C or altered enzyme activity has been implicated in the growth of breast and colon cancer cells, among other tumor types, and inhibition of KDM4 activity has been shown in some contexts to reduce cancer cell growth and proliferation [344-347].

FINDING SUMMARY
KDM4C encodes a histone demethylase, also known as Jumonji C domain-containing protein 2C (JMJDC2C), which functions to regulate transcription and gene expression by altering methylation patterns on histones [347].

GENE
MITF

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no available therapies to directly target MITF, but small-molecule inhibitors are in preclinical development [348-349]. Preclinical studies have reported that histone deacetylase (HDAC) inhibitors suppress MITF expression in melanoma and clear cell sarcoma cells, reduce cell proliferation, and sensitize the cells to other therapies, such as MAPK pathway inhibitors [350-351]. MITF has also been reported to transcriptionally activate MET [352-353], but it is not known if MITF alterations are associated with sensitivity to MET inhibitors; a clinical trial of the putative MET inhibitor tivantinib (ARQ 197) for MITF-associated tumors displayed only modest antitumor activity [354-356]. Preclinical data suggest that MITF overexpression confers resistance to MEK inhibitors in melanoma cells [357-358]. However, MITF amplification does not affect the sensitivity of melanoma cells to chemotherapeutic agents or the sensitivity of cells harboring BRAF V600E mutations to vemurafenib [359-360].

FREQUENCY & PROGNOSIS
In the TCGA datasets, MITF amplification was most frequently observed in melanoma (4.2%), uterine carcinosarcoma (3.5%), ovarian serous cystadenocarcinoma (2.1%), and pancreatic adenocarcinoma (1.6%) (cBioPortal, 2019). MITF amplification has been reported in 5–21% of melanoma samples and in 5–40% of melanoma cell lines analyzed [359,361-364], and MITF expression in melanoma cells has been reported to vary widely [365-367]. The significance of MITF alterations in tumor types other than melanoma have not been extensively studied, with the exception of clear cell sarcoma and a renal cell carcinoma subtype characterized by alterations in MITF-related transcription factors [368].

FINDING SUMMARY
MITF encodes microphthalmia-associated transcription factor, a protein required for pigment cell development [369]. Along with its role as a transcriptional activator, MITF plays a critical role in regulating cell cycle progression by interacting with RB1 [370]. MITF is commonly amplified in human melanomas and is considered an oncogene in this context [359,361]. Although the MITF E318K mutation has been demonstrated to activate MITF and is associated with germline predisposition to melanoma and renal cell carcinoma [371], characterization of other cancer-associated MITF mutations is lacking.

GENE
NOTCH1

ALTERATION
D1870N

POTENTIAL TREATMENT STRATEGIES

NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be potential therapeutic approaches in the case of NOTCH1 activating mutations [372-379]. Complete responses to the GSI BMS-906024 (AL101) were achieved in a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation [380] and in a patient with gastroesophageal junction adenocarcinoma harboring multiple NOTCH1 mutations, as well as a partial response in a patient with adenoid cystic carcinoma harboring a single NOTCH1 mutation[381]. BMS-906024 has been shown to have pan-NOTCH signaling inhibitory activity in vitro and anti-tumor efficacy in xenograft models of leukemia and triple-negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression [382]. On the basis of clinical data in non-Hodgkin lymphoma, NOTCH1 activating alterations may be associated with sensitivity to the FDA-approved PI3K inhibitor copanlisib [383]; this is further supported by limited preclinical data that suggest that NOTCH1 may be a negative regulator of PTEN [384-385]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the Sarcoma TCGA dataset, NOTCH1 mutation and homozygous deletion have been reported in 0.4% and 1.5% of samples analyzed, respectively (cBioPortal, Jan 2019). In one study, NOTCH1 mutation was reported in 1/25 sarcoma samples [386]. Although lower NOTCH1 protein levels were associated with advanced stage of angiosarcomas in one study [387], published clinical data on the prognostic implications of NOTCH1 alterations in soft tissue sarcomas are limited (PubMed, Dec 2018).

FINDING SUMMARY

NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene [388-389]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis [390-391]. NOTCH1 mutations leading to gamma-secretase inhibitor (GSI)-sensitive activation have been identified in the extracellular domain [392], heterodimerization domain (HD; amino acids 1571-1735) [393-397] and PEST domain (amino acids 2424-2555) [398] in multiple cancer types including T-cell acute lymphoblastic leukemia (T-ALL) [393]. However, this alteration has not been characterized and its effect on function is unclear, although it has been reported in the context of cancer, which may indicate biological relevance.

GENE
PAX5

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

There are no therapies available to target genomic alterations in PAX5. In pulmonary neuroendocrine tumors, particularly SCLC, PAX5 is coexpressed and colocalized with active MET [399-400], and a preclinical study of SCLC showed that PAX5 activates MET transcription [399]. This same study showed that combinatorial reduction of SCLC cell viability can be achieved by PAX5 knockdown and treatment with inhibitors of MET or topoisomerase 1 [399], although whether PAX5 mutations confer sensitivity to these inhibitors has not been evaluated.

FREQUENCY & PROGNOSIS

Compared with hematologic malignancies, PAX5 genomic alterations are rare in solid tumors and have not been extensively studied in this context (COSMIC, PubMed, 2017). However, it has been suggested that PAX5 is a tumor suppressor for various epithelial cancers, as transcriptional silencing of PAX5 by promoter methylation has been reported in multiple tumor types including non-small cell lung cancer, breast cancer, and head and neck squamous cell carcinoma [401-404]. In gastric cancer, PAX5 methylation is correlated with worse survival [405-406]. In contrast, PAX5 is believed to act as an oncogene in neuroendocrine tumors. PAX5 is frequently expressed in Merkel cell carcinoma, small cell lung carcinoma (SCLC), other pulmonary neuroendocrine carcinomas, and neuroblastoma [399-400,407-411].

FINDING SUMMARY

Paired box (PAX) genes such as PAX5 encode transcription factors that regulate cell differentiation and development. The protein PAX5 (also known as BSAP) is a master regulator of B-cell development [412-413]. PAX5 has been extensively studied in B-cell malignancies, particularly B-cell acute lymphoblastic leukemia (B-ALL), for which it has both oncogenic and tumor suppressive activities [413].

GENE
PCLO

ALTERATION
A915S - subclonal

POTENTIAL TREATMENT STRATEGIES
There are currently no therapies or clinical trials targeting alterations in PCLO.

FREQUENCY & PROGNOSIS
Although a mechanistic or prognostic role for piccolo has not been defined in cancer, mutations in PCLO have been found in up to 30% of tumors for some cancer types, particularly in adenocarcinomas of the lung, esophagus, and large intestine, and in up to 15% of diffuse large B cell lymphomas (DLBCL), plasma cell myelomas, and mantle cell lymphomas (COSMIC, PubMed, 2017)[414]. However, the ratio of nonsynonymous to synonymous mutations led researchers to suggest that many of these alterations may be passenger mutations of no significance in DLBCL.

FINDING SUMMARY
PCLO encodes the high-molecular weight protein piccolo, which is an important component of the presynaptic active zone in neurons and plays a role in neurotransmitter release [415].

GENE
PRKDC

ALTERATION
T1269M

POTENTIAL TREATMENT STRATEGIES
There are no therapies that have been shown to target PRKDC alterations in cancer. Preclinical studies have demonstrated synthetic lethal interactions between PRKDC and ATM [416] or MSH3 [417], and that inhibition of DNA-PK results in increased sensitivity to radiation or DNA damaging chemotherapies [418-419]; however, therapeutic targeting of cells with PRKDC loss-of-function alterations has not been demonstrated. High expression of DNA-PKcs has been correlated with resistance to radiotherapy in prostate cancer [420] and cervical cancer [421], but with better response to radiotherapy in breast cancer [422]. Preclinical studies have suggested that DNA-PKcs inhibition may potentiate treatment with chemotherapy or radiotherapy in cancer types with high DNA-PKcs expression such as CLL [423] or HCC [424].

FREQUENCY & PROGNOSIS
In the TCGA datasets, PRKDC mutation has been observed most frequently in stomach adenocarcinoma (11%)[121], endometrial carcinoma (9.7%)[52], and lung squamous cell carcinoma (9.6%)[425]; PRKDC amplification was detected most frequently in uterine carcinosarcoma (18%), prostate (15%)[426], breast (12%) [427], and uveal melanoma (8%)(cBioPortal, 2018). A CPQ-PRKDC fusion has been described in a endometrial cancer cell line, but this cell line was not dependent on the PRKDC fusion transcript [428]. Overexpression of DNA-PK has been observed in various cancer types [429-431] and has been associated with poor outcomes in chronic lymphocytic leukemia (CLL) [423,432], prostate cancer [433], HCC[424,434], non-small cell lung cancer [435], and breast cancer [436]. In contrast, other studies have suggested that loss of DNA-PK expression has been associated with poor outcome in gastric cancer [437] and patients with breast cancer [422,438].

FINDING SUMMARY
PRKDC encodes DNA-PKcs, which is the catalytic subunit of the DNA-dependent protein kinase complex (DNA-PK) that is involved in DNA repair by non-homologous end joining and homologous recombination [430]. DNA-PKcs may function as a tumor suppressor via maintenance of genomic stability; however, some studies have suggested a role for DNA-PKcs in promoting tumorigenesis by resistance to genotoxic chemotherapy or by transcriptional regulation of hormone receptor activity in breast and prostate cancer [430,433]. PRKDC missense mutations, truncation mutations, and fusions have been observed in the context of cancer but these alterations have not been characterized, and their significance in cancer has not been established [428-430,439]. PRKDC copy number increase has been correlated with PRKDC mRNA expression in one study of hepatocellular carcinoma (HCC) [424].

GENE
PTPN11

ALTERATION
V428M

POTENTIAL TREATMENT STRATEGIES

SHP-2 has been reported to activate the RAS-MEK-ERK, PI3K, and SRC kinase pathways [440-443]. Preclinical studies in hematologic and solid cancer cell lines[442,444-445] and in animal models of developmental abnormalities associated with Noonan syndrome and LEOPARD syndrome [446-448] have suggested that PTPN11 mutations may predict sensitivity to MEK or PI3K inhibitors. The MEK inhibitors trametinib and cobimetinib are approved to treat unresectable or metastatic BRAF V600E or V600K mutant melanoma [449-450]. Various MEK and PI3K inhibitors are under investigation in clinical trials. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

PTPN11 mutation has been observed in <1% of sarcomas (cBioPortal, COSMIC, Mar 2018). Published data investigating the prognostic implications of PTPN11 alterations in sarcoma are limited (PubMed, Mar 2018).

FINDING SUMMARY

PTPN11 encodes the protein tyrosine-protein phosphatase non-receptor type 11, also known as SHP-2. PTPN11 plays a critical role in both embryonic development and cancer [451]. PTPN11 is also known to be somatically mutated in a variety of cancers, where both oncogenic and tumor suppressor roles for PTPN11 have been described [452-454]. 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. Germline mutations in PTPN11 have been found in the developmental disorder Noonan syndrome, which predisposes individuals to various cancers, including embryonal rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia [455-460].

GENE
SMARCA4

ALTERATION
G1232D

POTENTIAL TREATMENT STRATEGIES

There are no therapies that directly address mutant SMARCA4 or loss of functional BRG1. However, on the basis of both clinical[461-462] and preclinical[462-463] data, patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with inhibitors of EZH2. In preclinical studies, cells with dual inactivation of SMARCA4 and SMARCA2, which is characteristic of SCCOHT [464-465], were sensitive to EZH2 inhibitors[462-463,466], and two patients with SCCOHT experienced clinical benefit (1 partial response, 1 long-term stable disease) upon treatment with the EZH2 inhibitor tazemetostat[461-462]. Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells [467]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B [468].

FREQUENCY & PROGNOSIS

SMARCA4 mutations have been reported in 0-3% of sarcoma cases in large datasets (COSMIC, cBioPortal, Nov 2017). SMARCA4/BRG1-deficiency has been associated with an aggressive subtype of thoracic sarcoma with a rhabdoid histology and male-predominance [469-471]. A study of epithelioid sarcoma did not find loss of BRG1 expression in any of the 23 analyzed cases [472]. Published data investigating the prognostic implications of SMARCA4 alterations in sarcomas are limited (PubMed, Dec 2018). Loss of BRG1 expression has been shown to correlate with a poor patient prognosis in some cancers, while in others, elevated BRG1 expression is associated with poor patient prognosis [473-474].

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling [475]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor [476]. Alterations in SMARCA4 that disrupt or remove the ARID1A-interaction domain (aa 476-587)[477], ATP-binding domain (aa 766-931), or the bromodomain (aa 1477-1547)[478] are predicted to result in loss of SMARCA4 function. Certain point mutations have also been characterized to inactivate SMARCA4 [479-480].

GENE
TP53

ALTERATION
R273H, R175H

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor AZD1775 [481-484], or p53 gene therapy and immunotherapeutics such as SGT-53 [485-489] and ALT-801[490]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246 [491-493]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% disease control rate[494]. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type [495]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer[496]. Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel[497]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage [489]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model [498].

FREQUENCY & PROGNOSIS

In the Sarcoma MSKCC dataset, TP53 deletion has been reported in 11% of cases [72]. Mutations of TP53 have been reported in 14% of soft tissue tumors analyzed in COSMIC, including 28% of angiosarcomas, 33% of leiomyosarcomas, and 11% of rhabdomyosarcomas (Oct 2018). TP53 alterations appear to lead to chromosomal instability and drive oncogenesis in soft tissue sarcomas [499]. One study of soft tissue sarcomas reported that TP53 non-frameshift mutations correlated with poor prognosis, including lymph node metastasis, increased rate of relapse, and decreased overall survival [500].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [501]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis [502-504]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers [505-507], including sarcomas [508-510]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000 [511] to 1:20,000 [510]. In the appropriate clinical context, germline testing of TP53 is recommended.

GENE
ZMYM3

ALTERATION
rearrangement exon 17

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies to address genomic alterations in ZMYM3.

FREQUENCY & PROGNOSIS

ZMYM3 mutations are rare in solid tumors and hematological cancers, being most frequently reported in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (2-4.3% of cases) [512].

FINDING SUMMARY

ZMYM3, also known as ZNF261, is a zinc-finger containing protein capable of binding to methylated histones [513]. ZMYM3 is a component of multi-protein complexes containing histone deacetylase activity that function to silence gene expression by modifying chromatin structure [514-515]. However, the role of ZMYM3 in cancer is not clear. Disruptions at the ZMYM3 locus have been linked to intellectual disability [516-517].

Larotrectinib

Assay findings association

NTRK1
A107V - subclonal,
rearrangement intron 6

AREAS OF THERAPEUTIC USE

Larotrectinib is a tyrosine kinase inhibitor that targets NTRK1, NTRK2, and NTRK3. It is FDA approved to treat 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, and have no satisfactory alternative treatments, or that have progressed following treatment.

GENE ASSOCIATION

Based on extensive clinical evidence in various solid tumors[65,518 66], NTRK fusions may predict sensitivity to larotrectinib. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, it is not known whether this therapeutic approach would be relevant.

SUPPORTING DATA

Analysis of combined data from several clinical trials, including the pediatric Phase 1/2 SCOUT trial, reported an ORR of 91% (29/32) in pediatric and adult patients with NTRK fusion-positive sarcomas; the ORR was 90% (9/10) in patients with infantile fibrosarcoma (IFS), 88% (15/17) in patients with other soft tissue sarcomas, and 100% (5/5) in patients with GIST[519]. The SCOUT trial included 5 patients (3 with IFS and 2 with other soft tissue sarcomas) that received larotectinib as a neoadjuvant treatment, and each patient achieved a PR prior to surgery; CR or near CR (>98%) was reached in 3 of these patients following surgery[71]. One of two patients with NTRK fusion-positive bone sarcoma treated with larotrectinib exhibited a PR[518].

Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved as second-line treatment for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma, recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy, hepatocellular carcinoma previously treated with sorafenib, adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after 3 or more prior lines of therapy, adult or pediatric primary mediastinal large B-cell lymphoma (PMBCL) that is refractory or has relapsed after 2 or more prior lines of therapy, PD-L1-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on 2 or more lines of therapy, PD-L1-positive recurrent or metastatic cervical cancer that has progressed on or after chemotherapy, and adult or pediatric recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). Pembrolizumab is also approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, as first-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK genomic alterations, and as first-line treatment in combination with carboplatin and paclitaxel or nab-paclitaxel for metastatic squamous NSCLC. It is also approved to treat patients with advanced urothelial carcinoma who are not eligible for any platinum-containing chemotherapy, who have PD-L1 positive tumors and are not eligible for cisplatin-containing chemotherapy, or who progress on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. A patient with cancer of unknown primary harboring CD274 amplification experienced lasting partial remission upon treatment with pembrolizumab[100]. PD-L1 expression in at least 50% of tumor cells was associated with a higher response rate and longer overall survival in patients with non-small cell lung cancer (NSCLC)[520-521]. One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and progression-free survival (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[103]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[104]. On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various microsatellite instability (MSI)-high or mismatch repair-deficient solid tumors[522-523 524-5259], MSI may predict sensitivity to pembrolizumab. On the basis of emerging clinical data in patients with non-small cell lung cancer[10,526 37], colorectal cancer[9], or melanoma[34] and case reports in endometrial cancer[38-39] and glioblastoma[40-41], high tumor mutational burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

SUPPORTING DATA

A Phase 2 study of pembrolizumab for patients with advanced soft tissue or bone sarcomas reported objective responses for 22% (2/9) of undifferentiated pleomorphic sarcoma (UPS) cases and 5% (1/19) of bone sarcoma cases[527]. Although objective responses were not seen for patients with leiomyosarcoma (LMS, 0/10), liposarcoma (LPS, 0/9), synovial sarcoma (0/10), Ewing sarcoma (0/13), or chondrosarcoma (CS, 0/6) at 8 weeks of therapy, three additional partial responses were recorded for cases with UPS, LPS, or CS after 20 weeks of pembrolizumab[527]. In a Phase 1b trial of pembrolizumab for PD-L1-positive advanced solid tumors, a patient with resected uterine LMS had a complete pathological response at all but one metastatic site[528]. Pembrolizumab combined with liposomal doxorubicin achieved prolonged stable disease for a patient with sarcoma[529].

Afatinib

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. In Phase 2 studies of afatinib, patients with EGFR-amplified NSCLC achieved an objective response rate of 20% (5/25) and a disease-control rate of 64% (16/25)[530], and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease[531].

SUPPORTING DATA

Afatinib has been primarily evaluated for the treatment of EGFR-mutant NSCLC, in which treatment with afatinib exhibited significant improvement in progression free survival (PFS) vs. chemotherapy treatments[125,532]. A Phase 2 trial of afatinib in patients with either EGFR or ERBB2 amplification and esophagogastric, biliary tract, urothelial tract, or gynecologic cancer reported a 5% (1/20) objective response rate, with complete response achieved in one patient and stable disease (SD) achieved in 8 patients; the authors concluded that afatinib activity as a single agent was encouraging[531]. A Phase 1 trial of afatinib in advanced cancer reported SD in 14/31 patients[533]. A Phase 1 study of afatinib combined with pemetrexed in patients with advanced solid tumors reported confirmed partial response in 3% (1/30) of patients and SD in 33% (10/30) of patients[534].

Atezolizumab

Assay findings association

CD274 (PD-L1)
amplification

Microsatellite status
MSI-High

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma who are not eligible for any platinum-containing therapy, who have PD-L1-positive tumors and are not eligible for cisplatin-containing chemotherapy, or who progress during or following platinum-based chemotherapy. It is also approved to treat patients with metastatic non-small cell lung cancer (NSCLC) who progressed on prior treatments and as a first line treatment in combination with bevacizumab, paclitaxel, and carboplatin for patients with metastatic non-squamous NSCLC without EGFR or ALK alterations.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangements, that lead to overexpression of PD-L1 may predict sensitivity to atezolizumab based on clinical evidence in multiple solid tumor types[92,171 535]. On the basis of emerging clinical data showing efficacy of atezolizumab alone or in combination with antiangiogenic therapy for patients with MSI-H colorectal cancer[3] or endometrial cancer[4], MSI-H status may predict sensitivity to atezolizumab. Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to anti-PD-L1 inhibitors such as atezolizumab. Although atezolizumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to atezolizumab[171,535 92]. On the basis of emerging clinical data in patients with urothelial carcinoma[33,35], non-small cell lung cancer (NSCLC)[526,536], or melanoma[34], high tumor mutational burden (TMB) may predict sensitivity to anti-PD-L1 therapies such as atezolizumab. In a retrospective analysis that included these 3 solid tumor types as well as 14 others, TMB ≥20 correlated with an objective response rate of ≥33% for patients treated with atezolizumab-based regimens; for those whose tumors harbored TMB ≥16 muts/Mb, atezolizumab improved duration of response relative to chemotherapy (29 vs. 6.2 months)[44].

SUPPORTING DATA

Atezolizumab has been studied primarily for the treatment of non-small cell lung cancer (NSCLC)[537-538 539-54092-93] and urothelial carcinoma[541-54233,543]. A study of atezolizumab as monotherapy for patients with advanced solid tumors reported a median progression-free survival (PFS) of 18 weeks and an overall response rate (ORR) of 21%, including confirmed responses in 26% (11/43) of melanomas, 13% (7/56) of renal cell carcinomas (RCC) and 13% (1/6) of colorectal cancers (CRCs)[93]. A Phase 1a study of atezolizumab reported an ORR of 15% (9/62), median PFS of 5.6 months, and median overall survival (OS) of 28.9 months for patients with clear cell RCC[544]. A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 42% (10/24) of patients; no dose-limiting toxicities were observed[545]. A Phase 1b study evaluated atezolizumab in combination with the MEK inhibitor cobimetinib for advanced solid tumors and enrolled 23 patients with CRC, who were mostly (22/23) KRAS-mutant; 17% (4/23) of these patients achieved objective partial responses, with three of the responders being mismatch repair (MMR)-proficient and one of them having unknown MMR status. In addition, stable disease was observed for 22% (5/23) of patients, and no dose-limiting toxicities were encountered[546].

Avelumab

Assay findings association

CD274 (PD-L1)
amplification

Microsatellite status
MSI-High

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with metastatic Merkel cell carcinoma and patients with advanced urothelial carcinoma who have progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as avelumab based on clinical evidence in multiple solid tumor types[171,547 548-549 92,550 535]. On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab. Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as avelumab. Although avelumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[171,535 92]. On the basis of emerging clinical data in patients with urothelial carcinoma[33], non-small cell lung cancer[526,536], or melanoma[34], high tumor mutational burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab.

SUPPORTING DATA

The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[549], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[551], urothelial carcinoma[552], mesothelioma[553], ovarian carcinoma[547], and breast cancer[548], and from avelumab combined with axitinib in renal cell carcinoma[554]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[547-548 549]. Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[555-556 557]. Phase 3 studies are evaluating avelumab with chemoradiotherapy alone (NCT02952586) or in combination with cetuximab (NCT02999087) in patients with locally advanced head and neck squamous cell carcinoma (Mar 2017).

Cemiplimab-rwlc

Assay findings association

CD274 (PD-L1)
amplification

Microsatellite status
MSI-High

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Cemiplimab-rwlc is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s). In multiple cancer types, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as improved clinical benefit in response to anti-PD-1 immunotherapies[103,520 104,521 558-559 101-102] and may predict sensitivity to cemiplimab-rwlc. On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[522-523 524-525 9,560 8], MSI-H status may predict sensitivity to cemiplimab-rwlc. On the basis of emerging clinical data in patients with non-small cell lung cancer[10,526 561], colorectal cancer[9], or melanoma[34] and case reports in endometrial cancer[38-39] and glioblastoma[41], high tumor mutational burden (TMB) may predict sensitivity to anti-PD-1 therapies, such as cemiplimab-rwlc.

SUPPORTING DATA

Cemiplimab-rwlc has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[562]. Clinical responses have also been reported in non-small cell lung cancer (40% ORR, 1 CR and 7 PRs) and basal cell carcinoma (1 PR)[563-564].

Cetuximab

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS wild-type metastatic colorectal cancer (CRC).

GENE ASSOCIATION

EGFR amplification or activating alteration may confer sensitivity to EGFR inhibitory antibodies such as cetuximab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[565].

SUPPORTING DATA

In a Phase 2 trial of cetuximab in patients with metastatic or advanced soft tissue or bone sarcoma, no clinical benefit was observed irrespective of MAPK, PTEN or phospho-EGFR status[566]. Two case studies have reported that a combination of gefitinib with the anti-EGFR antibody cetuximab achieved a durable partial response and tumor regression in two patients with recurrent chordomas[567-568]. Cetuximab exhibited some efficacy against cultured osteosarcoma cells[569-570].

Crizotinib

Assay findings association

NTRK1
A107V - subclonal,
rearrangement intron 6

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

GENE ASSOCIATION

Alterations that activate NTRK1 may predict sensitivity to crizotinib. Clinical benefit with crizotinib treatment has been achieved in patients NTRK1-fusion-positive tumors including infantile fibrosarcoma[60-61], lung adenocarcinoma[57], and undifferentiated pleomorphic sarcoma[571]. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, it is not known whether this therapeutic approach would be relevant.

SUPPORTING DATA

A patient with primary undifferentiated pleomorphic sarcoma harboring an LMNA-NTRK1 fusion was treated with crizotinib and exhibited a near complete response that was ongoing at 18 months[571]. Several small studies have reported clinical response to crizotinib in patients with inflammatory myofibroblastic tumors (IMTs)[572-573 574-575], smooth muscle tumor of uncertain malignant potential (STUMP)[576], alveolar soft parts sarcoma and alveolar rhabdomyosarcoma[577].

Dacomitinib

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations.

GENE ASSOCIATION

On the basis of clinical[578-579 580] and preclinical[581-582] data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

Clinical data on the efficacy of dacomitinib for the treatment of sarcoma are limited (PubMed, Oct 2018). Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months)[128,578]. A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification[580,583]. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS>4 months) in 13/31 (42%) of patients[584]. Studies of dacomitinib in esophageal[585] and cutaneous[586] SCC reported RRs of 12.5% (6/48) and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. On the other hand, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer[587] and patients with EGFR-amplified glioblastoma[588] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[587] and 15/49 (31%) in EGFR-amplified glioblastoma[588].

Durvalumab

Assay findings association

CD274 (PD-L1)
amplification

Microsatellite status
MSI-High

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy. Durvalumab is also approved to treat patients with unresectable, Stage 3 non-small cell lung cancer that has not progressed following concurrent platinum-based chemotherapy and radiation.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as durvalumab based on clinical evidence in multiple solid tumor types[171,547 548-549 94,550 98-99 96-9792,535 95]. On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab. Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as durvalumab. Although durvalumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[171,535 92]. On the basis of emerging clinical data in patients with urothelial carcinoma[33], non-small cell lung cancer[526,536], or melanoma[34], high tumor mutational burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as durvalumab.

SUPPORTING DATA

Single-agent durvalumab has demonstrated efficacy in urothelial carcinoma[94-95], non-small cell lung cancer[96-97], and head and neck squamous cell carcinoma[98,589]. In patients with advanced solid tumors, durvalumab monotherapy has elicited disease control rates (DCRs) of 36–46% (7/19 to 12/26) in Phase 1/2 studies[590-591]. Durvalumab is also under investigation in combination with other agents in Phase 1/2 trials. In advanced melanoma, durvalumab in combination with trametinib and dabrafenib elicited objective response rates (ORRs) and DCRs of 76% (16/21) and 100% (21/21) in patients with BRAF-mutant tumors, and durvalumab with trametinib elicited ORRs and DCRs of 21% (3/14) and 64% (9/14) in patients whose tumors were BRAF wild-type[523]. Durvalumab in combination with the PARP inhibitor olaparib has shown activity in patients with metastatic castration-resistant prostate cancer and progression on enzalutamide and/or abiraterone[592] and in patients with BRCA-wild-type breast or gynecological cancer[593]. Durvalumab in combination with the anti-CTLA4 antibody tremelimumab, but not durvalumab as a single-agent, has shown activity in patients with previously treated advanced germ cell tumors[594]. Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680[595], the CXCR2 antagonist AZD5069[596], or the ATR inhibitor AZD6738[597]. In patients with treatment-refractory solid tumors, concurrent durvalumab and radiotherapy achieved an ORR of 60% (6/10) for in-field evaluable lesions, including 2 complete and 4 partial responses[598].

Erlotinib

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved both as first-line and maintenance therapy, as well as second or greater line of treatment after chemotherapy failure, for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with advanced NSCLC receiving single-agent erlotinib or gefitinib, increased EGFR copy number associated with improved overall survival (hazard ratio [HR] = 0.77) in a meta-analysis, although the survival benefit was not observed for East Asian populations (HR = 1.11)[599-600 601].

SUPPORTING DATA

The approval of erlotinib in NSCLC is based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected NSCLC patients treated with erlotinib compared to standard chemotherapy[602]. Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for this class of medications compared with combination chemotherapy in patients with known EGFR mutations, including the EURTAC trial of erlotinib vs. platinum-based chemotherapy[123]. A Phase 3 clinical trial comparing erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer reported improved overall survival when compared to patients treated with gemcitabine alone (6.24 vs. 5.91 months)[603]. In breast cancer, erlotinib as a single therapy has been reported to have minimal efficacy[604]. A Phase 1 study of the combination therapy of erlotinib with capecitabine and docetaxel in patients with metastatic breast cancer reported an overall 67% response rate; however, the authors suggested that these results will require confirmation in larger, randomized studies[605]. A Phase 2 clinical trial of erlotinib in gastric adenocarcinoma reported no clinical responses, although there were no instances of EGFR mutation or amplification in this study group[606]. A Phase 2 study in patients with metastatic esophageal or gastroesophageal junction (GEJ) cancer reported partial responses in 8% (2/24) of patients with EGFR-positive tumors, but responses were only observed in patients with squamous cell carcinoma and not in patients with adenocarcinoma[607-608]. Erlotinib in combination with modified FOLFOX6 has shown activity in patients with metastatic or advanced esophageal or GEJ cancer, with 6.1% (2/33) and 45.5% (15/33) of evaluable patients exhibiting complete responses and partial responses, respectively[609]. A study of elderly patients with esophageal or GEJ carcinoma treated with erlotinib and radiation therapy reported an overall survival of 7.3 months[610].

Gefitinib

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[611-612 613-614 615-616 617]. For patients with advanced NSCLC receiving single-agent erlotinib or gefitinib, increased EGFR copy number associated with improved overall survival (hazard ratio [HR] = 0.77) in a meta-analysis, although the survival benefit was not observed for East Asian populations (HR = 1.11)[599-600 601]. Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[618-619].

SUPPORTING DATA

A Phase 1 study of the combination of gefitinib with the VEGFR-2 inhibitor cediranib reported partial responses for 9% (8/90) of patients, including 1 with osteosarcoma, and stable disease for 42% (38/90) of others[620]. A Phase 2 trial of gefitinib in patients with synovial sarcomas expressing EGFR and refractory to doxorubicin did not find significant clinical activity associated with gefitinib[621]. A Phase 1 trial of 29 pediatric patients with refractory solid tumors treated with gefitinib and irinotecan found that the combination was well tolerated and that gefitinib increased the bioavailability of irinotecan; this study recorded a partial response in one patient with Ewing sarcoma[622]. Case reports describe that gefitinib combined with the anti-EGFR antibody cetuximab achieved a durable partial response and tumor regression in two patients with recurrent chordomas[567-568].

Lapatinib

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

GENE ASSOCIATION

EGFR amplification or activation may confer sensitivity to EGFR/multi-tyrosine kinase inhibitors, such as lapatinib. A Phase 2 study of lapatinib in non-small cell lung cancer did not observe any responses for five patients with EGFR amplification[623].

SUPPORTING DATA

Clinical data on the efficacy of lapatinib for the treatment of sarcoma are limited (PubMed, Feb 2018). Investigations into the efficacy of lapatinib have primarily been in the context of breast cancer[624-625 626-627 628-629]. As first-line therapy for HER2+ metastatic breast cancer, lapatinib plus taxane resulted in shorter median progression-free survival (PFS) compared with trastuzumab plus taxane (9.0 vs. 11.3 months, hazard ratio of 1.37)[630]. For patients who have progressed on trastuzumab plus taxane, ado-trastuzumab emtansine (T-DM1) was superior to lapatinib plus capecitabine (overall survival (OS) of 30.9 vs. 25.1 months)[631]. In postmenopausal patients with hormone receptor-positive (HR+) HER2+ metastatic breast cancer, lapatinib combined with letrozole increased median PFS compared to letrozole alone (8.2 vs. 3.0 months)[632]. A Phase 2 study selecting patients with ERBB2-amplified solid tumors reported one complete response in a patient with esophageal adenocarcinoma[633]. Phase 1 studies evaluating lapatinib alone or in combination with chemotherapy agents reported partial responses in patients with various solid tumors and one complete response in a patient with EGFR-overexpressing head and neck squamous cell carcinoma[634-635 636-637]. In a Phase 1 trial of lapatinib plus pazopanib, one patient with a salivary gland tumor experienced a partial response[638].

Nivolumab

Assay findings association

CD274 (PD-L1)
amplification

Microsatellite status
MSI-High

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is FDA approved as adjuvant treatment for completely resected advanced melanoma and as treatment for unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved in combination with ipilimumab to treat intermediate- or poor-risk, previously untreated advanced renal cell carcinoma (RCC) and as monotherapy to treat advanced RCC after prior antiangiogenic therapy. Nivolumab is also approved to treat metastatic non-small cell lung cancer (NSCLC) after progression on prior treatments, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after progression on or after platinum-based therapy, advanced urothelial carcinoma after progression on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy, hepatocellular carcinoma (HCC) previously treated with sorafenib, classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin, and metastatic small cell lung cancer (SCLC) after progression on platinum-based chemotherapy and at least one other line of therapy. Furthermore, nivolumab is approved as both a single agent and in combination with ipilimumab to treat patients 12 years and older with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to nivolumab. In various advanced solid tumors, including melanoma, lung, kidney, prostate, and colorectal cancer, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as with objective response to nivolumab[104,559]. On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[8,560], MSI-H status may predict sensitivity to nivolumab. On the basis of emerging clinical data in patients with non-small cell lung cancer[10,526 561], colorectal cancer[9], or melanoma[34] and case reports in endometrial cancer[38-39] and glioblastoma[41], high tumor mutational burden (TMB) may predict sensitivity to anti-PD-1 therapies such as nivolumab.

SUPPORTING DATA

A retrospective analysis of nivolumab as a monotherapy or in combination with pazopanib for patients with previously treated metastatic sarcomas reported clinical benefit for 39% (9/23) of the overall cohort; two patients with dedifferentiated chondrosarcoma and intimal sarcoma experienced partial responses to nivolumab, and one case with epithelioid sarcoma responded to nivolumab plus pazopanib[639]. Nivolumab did not show antitumor activity for any of 12 genomically unselected patients with uterine leiomyosarcoma in a Phase 2 trial[640]; however, 3/7 patients with leiomyosarcoma were reported to benefit from regimens containing nivolumab in one study[639]. In a case study, nivolumab treatment elicited 6 months of regressive disease in a patient with PD-L1-positive leiomyosarcoma[641].

Panitumumab

Assay findings association

EGFR
amplification - equivocal

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy.

GENE ASSOCIATION

EGFR amplification or activating alteration may confer sensitivity to EGFR inhibitory antibodies such as panitumumab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[565].

SUPPORTING DATA

A Phase 1 study of panitumumab in combination with the anti-IGF-1R antibody ganitumab and the mTOR inhibitor everolimus, which included 5 patients with sarcoma, reported prolonged (>24 months) SD in one patient with chondrosarcoma[642].

Pembrolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved as second-line treatment for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma, recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy, hepatocellular carcinoma previously treated with sorafenib, adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after 3 or more prior lines of therapy, adult or pediatric primary mediastinal large B-cell lymphoma (PMBCL) that is refractory or has relapsed after 2 or more prior lines of therapy, PD-L1-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on 2 or more lines of therapy, PD-L1-positive recurrent or metastatic cervical cancer that has progressed on or after chemotherapy, and adult or pediatric recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). Pembrolizumab is also approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, as first-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK genomic alterations, and as first-line treatment in combination with carboplatin and paclitaxel or nab-paclitaxel for metastatic squamous NSCLC. It is also approved to treat patients with advanced urothelial carcinoma who are not eligible for any platinum-containing chemotherapy, who have PD-L1 positive tumors and are not eligible for cisplatin-containing chemotherapy, or who progress on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. A patient with cancer of unknown primary harboring CD274 amplification experienced lasting partial remission upon treatment with pembrolizumab[100]. PD-L1 expression in at least 50% of tumor cells was associated with a higher response rate and longer overall survival in patients with non-small cell lung cancer (NSCLC)[520-521]. One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and progression-free survival (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[103]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[104]. On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various microsatellite instability (MSI)-high or mismatch repair-deficient solid tumors[522-523 524-5259], MSI may predict sensitivity to pembrolizumab. On the basis of emerging clinical data in patients with non-small cell lung cancer[10,526 37], colorectal cancer[9], or melanoma[34] and case reports in endometrial cancer[38-39] and glioblastoma[40-41], high tumor mutational burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

SUPPORTING DATA

A Phase 2 study of pembrolizumab for patients with advanced soft tissue or bone sarcomas reported objective responses for 22% (2/9) of undifferentiated pleomorphic sarcoma (UPS) cases and 5% (1/19) of bone sarcoma cases[527]. Although objective responses were not seen for patients with leiomyosarcoma (LMS, 0/10), liposarcoma (LPS, 0/9), synovial sarcoma (0/10), Ewing sarcoma (0/13), or chondrosarcoma (CS, 0/6) at 8 weeks of therapy, three additional partial responses were recorded for cases with UPS, LPS, or CS after 20 weeks of pembrolizumab[527]. In a Phase 1b trial of pembrolizumab for PD-L1-positive advanced solid tumors, a patient with resected uterine LMS had a complete pathological response at all but one metastatic site[528]. Pembrolizumab combined with liposomal doxorubicin achieved prolonged stable disease for a patient with sarcoma[529].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. 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.

BIOMARKER

Microsatellite status

CATEGORY

MSI-High

RATIONALE

High microsatellite instability (MSI) and mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors.

NCT02091141

PHASE 2

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

TARGETS
ERBB3, ERBB2, EGFR, BRAF, MEK, SMO, ALK, RET, PD-L1

LOCATIONS: Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, Missouri, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington, Wisconsin

NCT03092323

PHASE 2

SU2C-SARC032: A Phase II Randomized Controlled Trial of Neoadjuvant Pembrolizumab With Radiotherapy and Adjuvant Pembrolizumab in Patients With High-Risk, Localized Soft Tissue Sarcoma of the Extremity

TARGETS
PD-1

LOCATIONS: California, Florida, Iowa, Maryland, Massachusetts, Michigan, Missouri, Camperdown (Australia), New York, North Carolina, Ohio, Pennsylvania, Montreal (Canada), Brisbane (Australia)

NCT03084471

PHASE 3

An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies.

TARGETS
PD-L1, CTLA-4

LOCATIONS: Alaska, California, District of Columbia, Florida, Georgia, Iowa, Michigan, Montana, Nebraska, Moncton (Canada), New Jersey, New York, Oklahoma, Brampton (Canada), Hamilton (Canada), Kingston (Canada), London (Canada), Newmarket (Canada), Toronto (Canada), Oregon, Greenfield Park (Canada), South Carolina, Tennessee, Texas, Virginia, Washington, Quebec (Canada), Besançon Cedex (France), Bordeaux Cedex (France), Brest (France), Dijon (France), Lille Cedex (France), Nice (France), Paris (France), Pierre Benite (France), Saint Herblain Cedex (France), Strasbourg Cedex (France), Toulouse (France), Tours CEDEX (France), Villejuif (France), Berlin (Germany), Bielefeld (Germany), Dresden (Germany), Duisburg (Germany), Erlangen (Germany), Essen (Germany), Guetersloh (Germany), Hamburg (Germany), Jena (Germany), Kiel (Germany), Lübeck (Germany), Muenster (Germany), Münster (Germany), Rostock (Germany), Stuttgart (Germany), Wiesbaden (Germany), Würzburg (Germany), Ancona (Italy), Arezzo (Italy), Avellino (Italy), Catania (Italy), Lecce (Italy), Meldola (Italy), Milano (Italy), Modena (Italy), Ravenna (Italy), Roma (Italy), Rozzano (Italy), Busan (Korea, Republic of), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Leiden (Netherlands), Basel (Switzerland), Genolier (Switzerland), London (United Kingdom), Newcastle (United Kingdom), Plymouth (United Kingdom), Sheffield (United Kingdom)

NCT02646748

PHASE 1

A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors

TARGETS
JAK1, PD-1, PI3K-delta

LOCATIONS: California, District of Columbia, Florida, Maryland, Massachusetts, Michigan, New York, North Carolina, Pennsylvania, Texas, Utah

CLINICAL TRIALS

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Illinois, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
VEGFA, MET, EGFR, PD-1

LOCATIONS: California, Colorado, Meldola (Italy), Villejuif (France), Illinois, Massachusetts, Michigan, Missouri, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia, Tampere (Finland)

NCT03264066

PHASE 2

A Phase II, Open-Label, Multicenter, Multicohort Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab in Patients With Solid Tumors

TARGETS
PD-L1, MEK

LOCATIONS: Kansas, New York, Tennessee, Kortrijk (Belgium), Nyíregyháza (Hungary), Seoul (Korea, Republic of), London (United Kingdom)

NCT01876511

PHASE 2

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

TARGETS
PD-1

LOCATIONS: California, Maryland, Ohio, Oregon, Pennsylvania

NCT03089645

PHASE 1

A Phase 1 First Time in Human Study to Evaluate the Safety, Pharmacokinetics and Immunogenicity of MEDI5083 Alone and in Combination With Durvalumab in Selected Advanced Solid Tumors

TARGETS
PD-L1, CD40

LOCATIONS: New Jersey, Rhode Island, Tennessee, Clayton (Australia), Melbourne (Australia), Randwick (Australia)

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

BIOMARKER
Tumor Mutational Burden

CATEGORY
TMB-High (40 Muts/Mb)

RATIONALE
High tumor mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors.

NCT02091141

PHASE 2

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

TARGETS
ERBB3, ERBB2, EGFR, BRAF, MEK, SMO, ALK, RET, PD-L1

LOCATIONS: Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, Missouri, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington, Wisconsin

NCT03092323

PHASE 2

SU2C-SARC032: A Phase II Randomized Controlled Trial of Neoadjuvant Pembrolizumab With Radiotherapy and Adjuvant Pembrolizumab in Patients With High-Risk, Localized Soft Tissue Sarcoma of the Extremity

TARGETS
PD-1

LOCATIONS: California, Florida, Iowa, Maryland, Massachusetts, Michigan, Missouri, Camperdown (Australia), New York, North Carolina, Ohio, Pennsylvania, Montreal (Canada), Brisbane (Australia)

NCT03084471

PHASE 3

An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies.

TARGETS
PD-L1, CTLA-4

LOCATIONS: Alaska, California, District of Columbia, Florida, Georgia, Iowa, Michigan, Montana, Nebraska, Moncton (Canada), New Jersey, New York, Oklahoma, Brampton (Canada), Hamilton (Canada), Kingston (Canada), London (Canada), Newmarket (Canada), Toronto (Canada), Oregon, Greenfield Park (Canada), South Carolina, Tennessee, Texas, Virginia, Washington, Quebec (Canada), Besançon Cedex (France), Bordeaux Cedex (France), Brest (France), Dijon (France), Lille Cedex (France), Nice (France), Paris (France), Pierre Benite (France), Saint Herblain Cedex (France), Strasbourg Cedex (France), Toulouse (France), Tours CEDEX (France), Villejuif (France), Berlin (Germany), Bielefeld (Germany), Dresden (Germany), Duisburg (Germany), Erlangen (Germany), Essen (Germany), Guetersloh (Germany), Hamburg (Germany), Jena (Germany), Kiel (Germany), Lübeck (Germany), Muenster (Germany), Münster (Germany), Rostock (Germany), Stuttgart (Germany), Wiesbaden (Germany), Würzburg (Germany), Ancona (Italy), Arezzo (Italy), Avellino (Italy), Catania (Italy), Lecce (Italy), Meldola (Italy), Milano (Italy), Modena (Italy), Ravenna (Italy), Roma (Italy), Rozzano (Italy), Busan (Korea, Republic of), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Leiden (Netherlands), Basel (Switzerland), Genolier (Switzerland), London (United Kingdom), Newcastle (United Kingdom), Plymouth (United Kingdom), Sheffield (United Kingdom)

NCT02646748

PHASE 1

A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors

TARGETS
JAK1, PD-1, PI3K-delta

LOCATIONS: California, District of Columbia, Florida, Maryland, Massachusetts, Michigan, New York, North Carolina, Pennsylvania, Texas, Utah

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Illinois, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

CLINICAL TRIALS

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
VEGFA, MET, EGFR, PD-1

LOCATIONS: California, Colorado, Meldola (Italy), Villejuif (France), Illinois, Massachusetts, Michigan, Missouri, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia, Tampere (Finland)

NCT03264066

PHASE 2

A Phase II, Open-Label, Multicenter, Multicohort Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab in Patients With Solid Tumors

TARGETS
PD-L1, MEK

LOCATIONS: Kansas, New York, Tennessee, Kortrijk (Belgium), Nyíregyháza (Hungary), Seoul (Korea, Republic of), London (United Kingdom)

NCT03089645

PHASE 1

A Phase 1 First Time in Human Study to Evaluate the Safety, Pharmacokinetics and Immunogenicity of MEDI5083 Alone and in Combination With Durvalumab in Selected Advanced Solid Tumors

TARGETS
PD-L1, CD40

LOCATIONS: New Jersey, Rhode Island, Tennessee, Clayton (Australia), Melbourne (Australia), Randwick (Australia)

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

NCT03126591

PHASE 1

An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients With Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma (STS) Who Have Failed Standard Treatments

TARGETS
PD-1, PDGFRA

LOCATIONS: New York, Pennsylvania, Leuven (Belgium), Herlev (Denmark), Villejuif Cedex (France)

GENE
CD274 (PD-L1)

ALTERATION
amplification

RATIONALE
CD274 (PD-L1) amplification or rearrangements that disrupt the 3' UTR may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L1 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L1 expression.

NCT02091141

PHASE 2

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

TARGETS
ERBB3, ERBB2, EGFR, BRAF, MEK, SMO, ALK, RET, PD-L1

LOCATIONS: Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, Missouri, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington, Wisconsin

NCT03092323

PHASE 2

SU2C-SARC032: A Phase II Randomized Controlled Trial of Neoadjuvant Pembrolizumab With Radiotherapy and Adjuvant Pembrolizumab in Patients With High-Risk, Localized Soft Tissue Sarcoma of the Extremity

TARGETS
PD-1

LOCATIONS: California, Florida, Iowa, Maryland, Massachusetts, Michigan, Missouri, Camperdown (Australia), New York, North Carolina, Ohio, Pennsylvania, Montreal (Canada), Brisbane (Australia)

NCT03084471

PHASE 3

An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies.

TARGETS
PD-L1, CTLA-4

LOCATIONS: Alaska, California, District of Columbia, Florida, Georgia, Iowa, Michigan, Montana, Nebraska, Moncton (Canada), New Jersey, New York, Oklahoma, Brampton (Canada), Hamilton (Canada), Kingston (Canada), London (Canada), Newmarket (Canada), Toronto (Canada), Oregon, Greenfield Park (Canada), South Carolina, Tennessee, Texas, Virginia, Washington, Quebec (Canada), Besançon Cedex (France), Bordeaux Cedex (France), Brest (France), Dijon (France), Lille Cedex (France), Nice (France), Paris (France), Pierre Benite (France), Saint Herblain Cedex (France), Strasbourg Cedex (France), Toulouse (France), Tours CEDEX (France), Villejuif (France), Berlin (Germany), Bielefeld (Germany), Dresden (Germany), Duisburg (Germany), Erlangen (Germany), Essen (Germany), Guetersloh (Germany), Hamburg (Germany), Jena (Germany), Kiel (Germany), Lübeck (Germany), Muenster (Germany), Münster (Germany), Rostock (Germany), Stuttgart (Germany), Wiesbaden (Germany), Würzburg (Germany), Ancona (Italy), Arezzo (Italy), Avellino (Italy), Catania (Italy), Lecce (Italy), Meldola (Italy), Milano (Italy), Modena (Italy), Ravenna (Italy), Roma (Italy), Rozzano (Italy), Busan (Korea, Republic of), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Leiden (Netherlands), Basel (Switzerland), Genolier (Switzerland), London (United Kingdom), Newcastle (United Kingdom), Plymouth (United Kingdom), Sheffield (United Kingdom)

NCT02646748

PHASE 1

A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors

TARGETS
JAK1, PD-1, PI3K-delta

LOCATIONS: California, District of Columbia, Florida, Maryland, Massachusetts, Michigan, New York, North Carolina, Pennsylvania, Texas, Utah

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
VEGFA, MET, EGFR, PD-1

LOCATIONS: California, Colorado, Meldola (Italy), Villejuif (France), Illinois, Massachusetts, Michigan, Missouri, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia, Tampere (Finland)

CLINICAL TRIALS

NCT03264066

PHASE 2

A Phase II, Open-Label, Multicenter, Multicohort Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab in Patients With Solid Tumors

TARGETS
PD-L1, MEK

LOCATIONS: Kansas, New York, Tennessee, Kortrijk (Belgium), Nyíregyháza (Hungary), Seoul (Korea, Republic of), London (United Kingdom)

NCT03089645

PHASE 1

A Phase 1 First Time in Human Study to Evaluate the Safety, Pharmacokinetics and Immunogenicity of MEDI5083 Alone and in Combination With Durvalumab in Selected Advanced Solid Tumors

TARGETS
PD-L1, CD40

LOCATIONS: New Jersey, Rhode Island, Tennessee, Clayton (Australia), Melbourne (Australia), Randwick (Australia)

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

NCT03126591

PHASE 1

An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients With Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma (STS) Who Have Failed Standard Treatments

TARGETS
PD-1, PDGFRA

LOCATIONS: New York, Pennsylvania, Leuven (Belgium), Herlev (Denmark), Villejuif Cedex (France)

NCT02419495

PHASE 1

Phase IB Study to Evaluate the Safety of Selinexor (KPT-330) in Combination With Multiple Standard Chemotherapy Agents in Patients With Advanced Malignancies

TARGETS
PD-1, XPO1, PARP

LOCATIONS: Texas

CLINICAL TRIALS

GENE
EGFR

ALTERATION
amplification - equivocal

RATIONALE
EGFR amplification or activating mutations may predict sensitivity to EGFR-targeted therapies. Several strategies to circumvent resistance are under investigation, including irreversible EGFR tyrosine kinase inhibitors and the use of HSP90 inhibitors.

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Illinois, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
VEGFA, MET, EGFR, PD-1

LOCATIONS: California, Colorado, Meldola (Italy), Villejuif (France), Illinois, Massachusetts, Michigan, Missouri, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia, Tampere (Finland)

NCT02451553

PHASE 1

Phase I/IB Multi-center Study of Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor Afatinib (BIBW 2992) in Combination With Capecitabine for Advanced Solid Tumors and Pancretico-Biliary Cancers

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Indiana, Washington

NCT02506517

PHASE 2

Molecular Basket Trial In Multiple Malignancies With Common Target Pathway Aberrancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Toronto (Canada)

NCT01552434

PHASE 1

A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT02942095

PHASE 1

A Phase I Study of Ixazomib and Erlotinib in Advanced Solid Tumor Patients

TARGETS
EGFR, 20S proteasome

LOCATIONS: Texas

GENE
NTRK1

ALTERATION
A107V - subclonal, rearrangement intron 6

RATIONALE
NTRK1 activating fusions may predict sensitivity to TRK inhibitors or crizotinib. 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.

NCT02568267

PHASE 2

An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Arizona, California, Napoli (Italy), Colorado, Connecticut, District of Columbia, Florida, Georgia, Hawaii, Illinois, Roma (Italy), Genova (Italy), Milano (Italy), Fuenlabrada (Spain), Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nevada, New Hampshire, Albury (Australia), Liverpool (Australia), New Lambton Heights (Australia), New York, North Carolina, Ohio, Oklahoma, Oregon, Candiolo (Italy), Orbassano (Italy), Torino (Italy), Bedford Park (Australia), Texas, Pisa (Italy), Perugia (Italy), Utah, Padova (Italy), Heidelberg (Australia), Virginia, Washington, Wisconsin, Bordeaux (France), Lille (France), Lyon (France), Marseille (France), Marseille cedex 5 (France), Montpellier cedex 5 (France), Paris (France), Paris cedex 15 (France), Toulouse (France), Villejuif cedex (France), Berlin (Germany), Dresden (Germany), Göttingen (Germany), Köln (Germany), Hong Kong (Hong Kong), Kowloon (Hong Kong), Shatin (Hong Kong), Aichi (Japan), Ehime (Japan), Fukuoka (Japan), Hyogo (Japan), Kashiwa-shi (Japan), Miyagi (Japan), Niigata (Japan), Osaka (Japan), Shizuoka (Japan), Cheongju-si (Korea, Republic of), Seoul (Korea, Republic of), Amsterdam (Netherlands), Leiden (Netherlands), Gdansk (Poland), Gliwice (Poland), Otwock (Poland), Poznań (Poland), Warszawa (Poland), Singapore (Singapore), Barcelona (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Chang Hua (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taipei City (Taiwan), Cambridge (United Kingdom), London (United Kingdom), Manchester (United Kingdom)

NCT02637687

PHASE 1/2

A Phase 1/2 Study of the Oral TRK Inhibitor LOXO101 (Larotrectinib) in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: California, Florida, Massachusetts, New York, Ohio, Tennessee, Texas, Washington, Parkville (Australia), Sydney (Australia), Montréal (Canada), Toronto (Canada), Copenhagen (Denmark), Paris (France), Villejuif (France), Berlin (Germany), Heidelberg (Germany), Stuttgart (Germany), Dublin (Ireland), Milano (Italy), Seoul (Korea, Republic of), Utrecht (Netherlands), Barcelona (Spain), Stockholm (Sweden), Zürich (Switzerland), Sutton (United Kingdom)

NCT02576431

PHASE 2

A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-Positive Tumors

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: California, Kashiwa (Japan), District of Columbia, Florida, Illinois, Massachusetts, New York, North Carolina, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington, West Virginia, Copenhagen (Denmark), Bordeaux Cedex (France), Dublin (Ireland), Seoul (Korea, Republic of), Porto (Portugal), Outram (Singapore), Barcelona (Spain), Madrid (Spain), London (United Kingdom), Southampton (United Kingdom)

NCT00585195

PHASE 1

Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of Pf-02341066, A C-met/Hgfr Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer

TARGETS
ALK, AXL, MET, ROS1, TRKA, TRKC

LOCATIONS: Nagoya (Japan), California, Kashiwa (Japan), Colorado, Sapporo (Japan), Akashi (Japan), Massachusetts, Michigan, New York, North Carolina, Ohio, Osakasayama (Japan), Pennsylvania, Vermont, Melbourne (Australia), Seoul (Korea, Republic of)

NCT03215511

PHASE 1/2

A Phase 1/ 2 Study of the TRK Inhibitor LOXO 195 in Adult Subjects With NTRK Fusion (Previously Treated) or Non-Fusion NTRK Altered Cancers

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: California, Colorado, Massachusetts, Randwick (Australia), New York, Oregon, Tennessee, Texas, Virginia, Washington, Copenhagen (Denmark), Villejuif cedex (France), Seoul (Korea, Republic of), Singapore (Singapore), Barcelona (Spain), Madrid (Spain)

CLINICAL TRIALS

NCT03093116

PHASE 1/2

A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: California, Colorado, Massachusetts, New York, Seoul (Korea, Republic of)

NCT02122913

PHASE 1

A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients With Solid Tumors

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: Colorado, Massachusetts, Ohio, Oregon, Pennsylvania, Tennessee, Texas

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

RATIONALE
PDCD1LG2 (PD-L2) amplification may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L2 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L2 expression.

NCT03092323

PHASE 2

SU2C-SARC032: A Phase II Randomized Controlled Trial of Neoadjuvant Pembrolizumab With Radiotherapy and Adjuvant Pembrolizumab in Patients With High-Risk, Localized Soft Tissue Sarcoma of the Extremity

TARGETS
PD-1

LOCATIONS: California, Florida, Iowa, Maryland, Massachusetts, Michigan, Missouri, Camperdown (Australia), New York, North Carolina, Ohio, Pennsylvania, Montreal (Canada), Brisbane (Australia)

NCT03084471

PHASE 3

An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies.

TARGETS
PD-L1, CTLA-4

LOCATIONS: Alaska, California, District of Columbia, Florida, Georgia, Iowa, Michigan, Montana, Nebraska, Moncton (Canada), New Jersey, New York, Oklahoma, Brampton (Canada), Hamilton (Canada), Kingston (Canada), London (Canada), Newmarket (Canada), Toronto (Canada), Oregon, Greenfield Park (Canada), South Carolina, Tennessee, Texas, Virginia, Washington, Quebec (Canada), Besançon Cedex (France), Bordeaux Cedex (France), Brest (France), Dijon (France), Lille Cedex (France), Nice (France), Paris (France), Pierre Benite (France), Saint Herblain Cedex (France), Strasbourg Cedex (France), Toulouse (France), Tours CEDEX (France), Villejuif (France), Berlin (Germany), Bielefeld (Germany), Dresden (Germany), Duisburg (Germany), Erlangen (Germany), Essen (Germany), Guetersloh (Germany), Hamburg (Germany), Jena (Germany), Kiel (Germany), Lübeck (Germany), Muenster (Germany), Münster (Germany), Rostock (Germany), Stuttgart (Germany), Wiesbaden (Germany), Würzburg (Germany), Ancona (Italy), Arezzo (Italy), Avellino (Italy), Catania (Italy), Lecce (Italy), Meldola (Italy), Milano (Italy), Modena (Italy), Ravenna (Italy), Roma (Italy), Rozzano (Italy), Busan (Korea, Republic of), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Leiden (Netherlands), Basel (Switzerland), Genolier (Switzerland), London (United Kingdom), Newcastle (United Kingdom), Plymouth (United Kingdom), Sheffield (United Kingdom)

NCT02646748

PHASE 1

A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors

TARGETS
JAK1, PD-1, PI3K-delta

LOCATIONS: California, District of Columbia, Florida, Maryland, Massachusetts, Michigan, New York, North Carolina, Pennsylvania, Texas, Utah

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
VEGFA, MET, EGFR, PD-1

LOCATIONS: California, Colorado, Meldola (Italy), Villejuif (France), Illinois, Massachusetts, Michigan, Missouri, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia, Tampere (Finland)

NCT03264066

PHASE 2

A Phase II, Open-Label, Multicenter, Multicohort Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab in Patients With Solid Tumors

TARGETS
PD-L1, MEK

LOCATIONS: Kansas, New York, Tennessee, Kortrijk (Belgium), Nyíregyháza (Hungary), Seoul (Korea, Republic of), London (United Kingdom)

NCT03089645

PHASE 1

A Phase 1 First Time in Human Study to Evaluate the Safety, Pharmacokinetics and Immunogenicity of MEDI5083 Alone and in Combination With Durvalumab in Selected Advanced Solid Tumors

TARGETS
PD-L1, CD40

LOCATIONS: New Jersey, Rhode Island, Tennessee, Clayton (Australia), Melbourne (Australia), Randwick (Australia)

CLINICAL TRIALS

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

NCT03126591

PHASE 1

An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients With Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma (STS) Who Have Failed Standard Treatments

TARGETS
PD-1, PDGFRA

LOCATIONS: New York, Pennsylvania, Leuven (Belgium), Herlev (Denmark), Villejuif Cedex (France)

NCT02419495

PHASE 1

Phase IB Study to Evaluate the Safety of Selinexor (KPT-330) in Combination With Multiple Standard Chemotherapy Agents in Patients With Advanced Malignancies

TARGETS
PD-1, XPO1, PARP

LOCATIONS: Texas

NCT03010176

PHASE 1

Phase 1 Open Label, Multicenter Study of MK-1454 Administered by Intratumoral Injection as Monotherapy and in Combination With Pembrolizumab for Patients With Advanced/Metastatic Solid Tumors or Lymphomas

TARGETS
STING, PD-1

LOCATIONS: California, New York, Texas, Villejuif (France), Ramat Gan (Israel), London (United Kingdom)

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.

AKT1
K420del

AKT2
P115fs*33

ARAF
G245S

ATM
R2719H

BRIP1
V607G

CAD
K841N and R781H

CBL
T129fs*2

CCT6B
V367G

CIITA
Y34C

CREBBP
A1603T, T2434M, and V95M

DNM2
D215N

DNMT3A
R458Q

FBXO31
D347N

FGF3
R104*

FGFR2
R190Q

FGFR4
A229T

FHIT
amplification

GNA11
G208fs*16

HDAC7
A299T

HRAS
R73H

IKBKE
A410V

IRS2
R970Q

KDM5A
G8fs*58

KDM5C
K370N

KMT2C (MLL3)
R841W

LRP1B
M131I

LRRK2
N59K

MLL2
R2847H

NCOR2
A1010T and A832T

NF1
H389R

PBRM1
amplification

PC
A22T

PDGFRA
R764C

PTPRO
A11S

RARA
P440L

S1PR2
V195A

SETD2
N1733T

SF3B1
R397H

SGK1
V411I

SPEN
R1917H

STAG2
V1171A

U2AF1
V101A

VHL
amplification

WDR90
R218C

ZNF703
A500fs*43 and G439V

APPENDIX Genes Assayed in FoundationOne®Heme

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies, sarcomas, and pediatric cancers 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*	*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*
B2M	*BAP1*	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*
BCL7A	*BCOR*	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*
BRD4	*BRIP1*	*BRSK1*	*BTG2*	*BTK*	*BTLA*	*C11orf30 (EMSY)*	*CAD*
*CALR**	*CARD11*	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*
CCT6B	*CD22*	*CD274 (PD-L1)*	*CD36*	*CD58*	*CD70*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1B*	*CDKN2A*
CDKN2B	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*	*CIITA*
CKS1B	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*
EGFR	*ELP2*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*
ERBB3	*ERBB4*	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*
FAF1	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*	*FANCG*
FANCL	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FHIT	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*	*FOXO1*
FOXO3	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4 (C17orf39)*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*
GTSE1	*HDAC1*	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*
HIST1H2AC	*HIST1H2AG*	*HIST1H2AL*	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*
HIST1H3B	*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*	*IDH1*	*IDH2*
IGF1R	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*	*INPP4B*
INPP5D (SHIP)	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*
KDR	*KEAP1*	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*
LEF1	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*
MDM2	*MDM4*	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*
MITF	*MKI67*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*
MTOR	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*
NCSTN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*	*NOTCH1*
NOTCH2	*NPM1*	*NRAS*	*NTSC2*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*
NUP98	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*	*PBRM1*
PC	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*
PTPN11	*PTPN2*	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*
RARA	*RASGEF1A*	*RB1*	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*S1PR2*	*SDHA*	*SDHB*	*SDHC*	*SDHD*
SERP2	*SETBP1*	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA1*
SMARCA4	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*	*SOCS1*	*SOCS2*	*SOCS3*
SOX10	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*	*STAG2*	*STAT3*
STAT4	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*	*TAF1*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	*TMSB4XP8 (TMSL3)*
TNFAIP3	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*	*TRAF2*
TRAF3	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*
U2AF2	*VHL*	*WDR90*	*WHSC1 (MMSET or NSD2)*	*WISP3*	*WT1*	*XBP1*	*XPO1*
YY1AP1	*ZMYM3*	*ZNF217*	*ZNF24 (ZSCAN3)*	*ZNF703*	*ZRSR2*		

*Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR

APPENDIX Genes Assayed in FoundationOne®Heme

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26 (GRAF)*	
ARHGEF12	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*	*BCL10*	*BCL11A*
BCL11B	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*	*BCR*	*BIRC3*
BRAF	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CHIC2*	*CHN1*	*CIC*	*CIITA*	*CLP1*
CLTC	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*
CTNNB1	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*	*EGFR*	*EIF4A2*	*ELF4*
ELL	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*
FGFR1OP	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*	*FOXO4*	*FOXP1*
FSTL3	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*	*HEY1*	*HIP1*
HIST1H4I	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*	*HOXA9*	*HOXC11*
HOXC13	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*	*IGL*	*IKZF1*
IL21R	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*	*JAZF1*	*KAT6A (MYST3)*
KDSR	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*	*LPP*	*LYL1*
MAF	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1 (ENL)*	*MLLT10 (AF10)*
MLLT3	*MLLT4 (AF6)*	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*
MYC	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*	*NF2*
NFKB2	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*
NUMA1	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*	*PAFAH1B2*	*PAX3*	*PAX5*
PAX7	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*	*PDE4DIP*	*PDGFB*	*PDGFRA*	*PDGFRB*
PER1	*PHF1*	*PICALM*	*PIM1*	*PLAG1*	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*
PRDM16	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*	*RABEP1*	*RAF1*	*RALGDS*	*RAP1GDS1*
RARA	*RBM15*	*RET*	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*
RUNX1T1 (ETO)	*RUNX2*	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*
SNX29 (RUNDC2A)	*SRSF3*	*SS18*	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*STL*	*SYK*
TAF15	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*
TFG	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*
TPM3	*TPM4*	*TRIM24*	*TRIP11*	*TTL*	*TYK2*	*USP6*	*WHSC1 (MMSET or NSD2)*	
WHSC1L1	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*			

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

The median exon coverage for this sample is 853x

ACCURACY		
Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8% copies	>95.0%
Sensitivity: Microsatellite status	At ≥20% tumor nuclei	97.0%
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite status	Positive Predictive Value (PPV)	>95.0%
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

Assay specifications were determined for pical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne Heme test. Microsatellite status is assayed for all FoundationOne Heme samples and may be reported as "MSI-High", "MSI-Intermediate", "MS-Stable", or "Cannot Be Determined". Microsatellite status is reported as "Cannot Be Determined" if the sample is not of sufficient quality to be confidently determined.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne and FoundationOne Heme tests and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne and FoundationOne Heme samples and may be reported as “TMB-High”, “TMB-Intermediate”, “TMB-Low”, or “Cannot Be Determined”. TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to fewer than or equal to 5 Muts/Mb. Tumor Mutational Burden is reported as “Cannot Be Determined” if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

ABOUT FOUNDATIONONE HEME

FoundationOne Heme is a comprehensive genomic profiling test for hematologic malignancies, sarcomas and pediatric cancers. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across more than 250 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas, pediatric cancers.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

THE REPORT

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

Diagnostic Significance

FoundationOne Heme 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 FoundationOne Heme 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 Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Alterations and Therapies

Biomarker Findings

Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings

Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies

Sensitizing therapies → Resistant therapies. (If multiple therapies exist within any of these categories, they are listed alphabetically by therapy name.)

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

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 Heme.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Heme Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.

CE

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

1 (2007) Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 50 (1):113-30

2 Lal N, Beggs AD, Willcox BE, et al. (2015) An immunogenomic stratification of colorectal cancer: Implications for development of targeted immunotherapy. Oncoimmunology 4 (3):e976052

3 Hochster et al., 2017; ASCO Abstract 673

4 Fleming et al., 2018; ASCO Abstract 5585

5 Bang et al., 2018; ASCO Abstract 92

6 Gatalica Z, Snyder C, Maney T, et al. (2014) Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol. Biomarkers Prev. ePub Dec 2014

7 Overman et al., 2016; ASCO Abstract 3501

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