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
10 Trials *see p. 27*		Nivolumab
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.

CLINICAL TRIALS

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

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

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

8 Lipson EJ, Sharfman WH, Drake CG, et al. (2013) Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin. Cancer Res. 19 (2):462-8

9 Le DT, Uram JN, Wang H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N. Engl. J. Med. ePub Jun 2015

10 Rizvi NA, Hellmann MD, Snyder A, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science ePub Apr 2015

11 Monument MJ, Lessnick SL, Schiffman JD, et al. (2012) Microsatellite instability in sarcoma: fact or fiction? ISRN Oncol ePub 2012

12 Bonneville R, Krook MA, Kautto EA, et al. (2017) Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol 2017

13 Wooster R, Cleton-Jansen AM, Collins N, et al. (1994) Instability of short tandem repeats (microsatellites) in human cancers. Nat. Genet. 6 (2):152-6

14 Kawaguchi K, Oda Y, Takahira T, et al. (2005) Microsatellite instability and hMLH1 and hMSH2 expression analysis in soft tissue sarcomas. Oncol. Rep. 13 (2):241-6

15 Saito T, Oda Y, Kawaguchi K, et al. (2003) Possible association between tumor-suppressor gene mutations and hMSH2/hMLH1 inactivation in alveolar soft part sarcoma. Hum. Pathol. 34 (9):841-9

16 Suwa K, Ohmori M, Miki H (1999) Microsatellite alterations in various sarcomas in Japanese patients. J Orthop Sci 4 (3):223-30

17 Garcia JJ, Kramer MJ, O'Donnell RJ, et al. (2006) Mismatch repair protein expression and microsatellite instability: a comparison of clear cell sarcoma of soft parts and metastatic melanoma. Mod. Pathol. 19 (7):950-7

18 Aue G, Hedges LK, Schwartz HS, et al. (1998) Clear cell sarcoma or malignant melanoma of soft parts: molecular analysis of microsatellite instability with clinical correlation. Cancer Genet. Cytogenet. 105 (1):24-8

19 Rucińska M, Kozłowski L, Pepiński W, et al. (2005) High grade sarcomas are associated with microsatellite instability (chromosom 12) and loss of heterozygosity (chromosom 2). Med. Sci. Monit. 11 (2):BR65-8

20 Kocarnik JM, Shiovitz S, Phipps AI (2015) Molecular phenotypes of colorectal cancer and potential clinical applications. Gastroenterol Rep (Oxf) 3 (4):269-76

21 You JF, Buhard O, Ligtenberg MJ, et al. (2010) Tumours with loss of MSH6 expression are MSI-H when screened with a pentaplex of five mononucleotide repeats. Br. J. Cancer ePub Dec 2010

22 Bairwa NK, Saha A, Gochhait S, et al. (2014) Microsatellite instability: an indirect assay to detect defects in the cellular mismatch repair machinery. Methods Mol. Biol. ePub 2014

23 Boland CR, Thibodeau SN, Hamilton SR, et al. (1998) A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 58 (22):5248-57

24 Pawlik TM, Raut CP, Rodriguez-Bigas MA (2004) Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers 20 (4-5):199-206

25 Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. Gastroenterology ePub Jun 2010

26 Lynch HT, Lynch PM, Lanspa SJ, et al. (2009) Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. ePub Jul 2009

27 Pande M, Wei C, Chen J, et al. (2012) Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. Fam. Cancer ePub Sep 2012

28 Kastrinos F, Syngal S (2007) Recently identified colon cancer predispositions: MYH and MSH6 mutations. Semin. Oncol. 34 (5):418-24

29 Silva FC, Valentin MD, Ferreira Fde O, et al. (2009) Mismatch repair genes in Lynch syndrome: a review. Sao Paulo Med J ePub Jan 2009

30 Sehgal R, Sheahan K, O'Connell PR, et al. (2014) Lynch syndrome: an updated review. Genes (Basel) 5 (3):497-507

31 (2005) The incidence of Lynch syndrome. Fam. Cancer 4 (3):233-7

32 Snyder A, Makarov V, Merghoub T, et al. (2014) Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. ePub Dec 2014

33 Rosenberg JE, Hoffman-Censits J, Powles T, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet ePub May 2016

34 Johnson DB, Frampton GM, Rioth MJ, et al. (2016) Targeted Next Generation Sequencing Identifies Markers of Response to PD-1 Blockade. Cancer Immunol Res ePub Nov 2016

35 Balar AV, Galsky MD, Rosenberg JE, et al. (2017) Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet ePub 01 2017

36 Miao D, Margolis CA, Vokes NI, et al. (2018) Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. Nat. Genet. ePub Sep 2018

37 Dong ZY, Zhong WZ, Zhang XC, et al. (2017) Clin. Cancer Res. 23 (12):3012-3024

38 Mehnert JM, Panda A, Zhong H, et al. (2016) Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. J. Clin. Invest. ePub Jun 2016

39 Santin AD, Bellone S, Buza N, et al. (2016) Regression of Chemotherapy-Resistant Polymerase ε (POLE) Ultra-Mutated and MSH6 Hyper-Mutated Endometrial Tumors with Nivolumab. Clin. Cancer Res. 22 (23):5682-5687

40 Johanns TM, Miller CA, Dorward IG, et al. (2016) Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline POLE Deficiency Treated with Checkpoint Blockade Immunotherapy. Cancer Discov ePub 11 2016

41 Bouffet E, Larouche V, Campbell BB, et al. (2016) Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J. Clin. Oncol. ePub Jul 2016

42 Fabrizio DA, George TJ, Dunne RF, et al. (2018) Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. J Gastrointest Oncol 9 (4):610-617

43 Van Allen EM, Miao D, Schilling B, et al. (2015) Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science ePub Oct 2015

44 Legrand et al., 2018; ASCO Abstract 12000

45 Chalmers ZR, Connelly CF, Fabrizio D, et al. (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med ePub 04 2017

46 Lim J, Poulin NM, Nielsen TO (2015) New Strategies in Sarcoma: Linking Genomic and Immunotherapy Approaches to Molecular Subtype. Clin. Cancer Res. 21 (21):4753-9

47 Brohl AS, Solomon DA, Chang W, et al. (2014) The genomic landscape of the Ewing Sarcoma family of tumors reveals recurrent STAG2 mutation. PLoS Genet. ePub Jul 2014

48 Chen X, Stewart E, Shelat AA, et al. (2013) Targeting oxidative stress in embryonal rhabdomyosarcoma. Cancer Cell ePub Dec 2013

49 Pfeifer GP, You YH, Besaratinia A (2005) Mutations induced by ultraviolet light. Mutat. Res. 571 (1-2):19-31

50 Hill VK, Gartner JJ, Samuels Y, et al. (2013) The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet ePub 2013

51 Pfeifer GP, Denissenko MF, Olivier M, et al. (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene 21 (48):7435-51

52 Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. (2013) Integrated genomic characterization of endometrial carcinoma. Nature ePub May 2013

53 Briggs S, Tomlinson I (2013) Germline and somatic polymerase ε and δ mutations define a new class of hypermutated colorectal and endometrial cancers. J. Pathol. ePub Jun 2013

54 Heitzer E, Tomlinson I (2014) Replicative DNA polymerase mutations in cancer. Curr. Opin. Genet. Dev. ePub Feb 2014

55 (2012) Comprehensive molecular characterization of human colon and rectal cancer. Nature ePub Jul 2012

56 Roberts SA, Gordenin DA (2014) Hypermutation in human cancer genomes: footprints and mechanisms. Nat. Rev. Cancer ePub 12 2014

57 Vaishnavi A, Capelletti M, Le AT, et al. (2013) Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat. Med. ePub Nov 2013

58 Doebele RC, Davis LE, Vaishnavi A, et al. (2015) An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov ePub Oct 2015

59 Tatematsu T, Sasaki H, Shimizu S, et al. (2014) Mol Clin Oncol 2 (5):725-730

60 Wong V, Pavlick D, Brennan T, et al. (2016) Evaluation of a Congenital Infantile Fibrosarcoma by Comprehensive Genomic Profiling Reveals an LMNA-NTRK1 Gene Fusion Responsive to Crizotinib. J. Natl. Cancer Inst. ePub Jan 2016

61 Mody RJ, Wu YM, Lonigro RJ, et al. (2015) Integrative Clinical Sequencing in the Management of Refractory or Relapsed Cancer in Youth. JAMA ePub Sep 2015

62 Sartore-Bianchi A, Ardini E, Bosotti R, et al. (2016) Sensitivity to Entrectinib Associated With a Novel LMNA-NTRK1 Gene Fusion in Metastatic Colorectal Cancer. J. Natl. Cancer Inst. ePub Jan 2016

63 Farago AF, Le LP, Zheng Z, et al. (2015) Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol ePub Dec 2015

64 Drilon A, Siena S, Ou SI, et al. (2017) Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov ePub 04 2017

65 Drilon A, Laetsch TW, Kummar S, et al. (2018) Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N. Engl. J. Med. ePub 02 2018

66 Laetsch TW, DuBois SG, Mascarenhas L, et al. (2018) Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. ePub May 2018

67 Demetri et al., 2018; ESMO Abstract LBA17

68 Drilon A, Nagasubramanian R, Blake JF, et al. (2017) A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. Cancer Discov ePub 09 2017

69 Drilon A, Li G, Dogan S, et al. (2016) What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). Ann. Oncol. ePub 05 2016

70 Drilon A, Ou SI, Cho BC, et al. (2018) Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent- Front Mutations. Cancer Discov ePub Aug 2018

71 DuBois SG, Laetsch TW, Federman N, et al. (2018) The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer ePub Nov 2018

72 Barretina J, Taylor BS, Banerji S, et al. (2010) Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat. Genet. ePub Aug 2010

73 Bianchi E, Artico M, Di Cristofano C, et al. (null) Growth factors, their receptor expression and markers for proliferation of endothelial and neoplastic cells in human osteosarcoma. Int J Immunopathol Pharmacol 26 (3):621-32

74 Donovan MJ, Hempstead BL, Horvath C, et al. (1993) Immunohistochemical localization of Trk receptor protein in pediatric small round blue cell tumors. Am. J. Pathol. 143 (6):1560-7

75 Nogueira E, Navarro S, Pellín A, et al. (1997) Activation of TRK genes in Ewing's sarcoma. Trk A receptor expression linked to neural differentiation. Diagn. Mol. Pathol. 6 (1):10-6

76 Jung EJ, Kim DR (2008) Apoptotic cell death in TrkA-overexpressing cells: kinetic regulation of ERK phosphorylation and caspase-7 activation. Mol. Cells 26 (1):12-7

77 Klein R, Jing SQ, Nanduri V, et al. (1991) The trk proto-oncogene encodes a receptor for nerve growth factor. Cell 65 (1):189-97

78 Wooten MW, Seibenhener ML, Mamidipudi V, et al. (2001) The atypical protein kinase C-interacting protein p62 is a scaffold for NF-kappaB activation by nerve growth factor. J. Biol. Chem. 276 (11):7709-12

79 Stephens RM, Loeb DM, Copeland TD, et al. (1994) Trk receptors use redundant signal transduction pathways involving SHC and PLC-gamma 1 to mediate NGF responses. Neuron 12 (3):691-705

80 Tacconelli A, Farina AR, Cappabianca L, et al. (2004) TrkA alternative splicing: a regulated tumor-promoting switch in human neuroblastoma. Cancer Cell 6 (4):347-60

81 Martin-Zanca D, Hughes SH, Barbacid M (null) A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. Nature 319 (6056):743-8

82 Greco A, Miranda C, Pierotti MA (2010) Rearrangements of NTRK1 gene in papillary thyroid carcinoma. Mol. Cell. Endocrinol. ePub May 2010

83 Beimfohr C, Klugbauer S, Demidchik EP, et al. (1999) NTRK1 re-arrangement in papillary thyroid carcinomas of children after the Chernobyl reactor accident. Int. J. Cancer 80 (6):842-7

84 Butti MG, Bongarzone I, Ferraresi G, et al. (1995) A sequence analysis of the genomic regions involved in the rearrangements between TPM3 and NTRK1 genes producing TRK oncogenes in papillary thyroid carcinomas. Genomics 28 (1):15-24

85 Wiesner T, He J, Yelensky R, et al. (2014) Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. Nat Commun ePub 2014

86 Vaishnavi A, Le AT, Doebele RC (2015) TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov ePub Jan 2015

87 Arevalo JC, Conde B, Hempstead BL, et al. (2000) TrkA immunoglobulin-like ligand binding domains inhibit spontaneous activation of the receptor. Mol. Cell. Biol. 20 (16):5908-16

88 Reuther GW, Lambert QT, Caligiuri MA, et al. (2000) Identification and characterization of an activating TrkA deletion mutation in acute myeloid leukemia. Mol. Cell. Biol. 20 (23):8655-66

89 Coulier F, Martin-Zanca D, Ernst M, et al. (1989) Mechanism of activation of the human trk oncogene. Mol. Cell. Biol. 9 (1):15-23

90 Russo M, Misale S, Wei G, et al. (2016) Acquired Resistance to the TRK Inhibitor Entrectinib in Colorectal Cancer. Cancer Discov ePub Jan 2016

91 Martin-Liberal et al., 2015; ESMO Symposium on Immuno-Oncology Abstract 24P

92 Fehrenbacher L, Spira A, Ballinger M, et al. (2016) Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet ePub Apr 2016

93 Herbst RS, Soria JC, Kowanetz M, et al. (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature ePub Nov 2014

94 Powles et al., 2017; ASCO Genitourinary Abstract 286

95 Massard C, Gordon MS, Sharma S, et al. (2016) Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J. Clin. Oncol. ePub Sep 2016

96 Bais et al., 2017; AACR Abstract 3720/5

97 Garassino et al., 2016; IASLC Abstract PLO4a.03

98 Segal et al., 2015; ASCO Abstract 3011

99 Rebelatto et al., 2015; ASCO Abstract 8033

100 Gröschel S, Bommer M, Hutter B, et al. (2016) Cold Spring Harb Mol Case Stud 2 (6):a001180

101 Ansell et al., 2015; ASH Abstract 583

102 Ansell SM, Lesokhin AM, Borrello I, et al. (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N. Engl. J. Med. ePub Jan 2015

103 Kefford et al., 2014; ASCO Abstract 3005

104 Taube JM, Klein A, Brahmer JR, et al. (2014) Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin. Cancer Res. 20 (19):5064-74

105 Sharma et al., 2018; AACR abstract CT178

106 Green MR, Monti S, Rodig SJ, et al. (2010) Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood ePub Oct 2010

107 Derenzini E, Lemoine M, Buglio D, et al. (2011) The JAK inhibitor AZD1480 regulates proliferation and immunity in Hodgkin lymphoma. Blood Cancer J ePub Dec 2011

108 Movva S, Wen W, Chen W, et al. (2015) Multi-platform profiling of over 2000 sarcomas: identification of biomarkers and novel therapeutic targets. Oncotarget ePub May 2015

109 D'Angelo SP, Shoushtari AN, Agaram NP, et al. (2015) Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. Hum. Pathol. ePub Mar 2015

110 (1991) Preparing illustrations for half-tone reproduction. 1952. J Audiov Media Med 14 (1):35-8

111 Hino R, Kabashima K, Kato Y, et al. (2010) Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 116 (7):1757-66

112 Thompson RH, Gillett MD, Cheville JC, et al. (2004) Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. Proc. Natl. Acad. Sci. U.S.A. 101 (49):17174-9

113 Thompson RH, Kuntz SM, Leibovich BC, et al. (2006) Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 66 (7):3381-5

114 Hamanishi J, Mandai M, Iwasaki M, et al. (2007) Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc. Natl. Acad. Sci. U.S.A. 104 (9):3360-5

115 Kim JR, Moon YJ, Kwon KS, et al. (2013) Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. PLoS ONE ePub 2013

116 Keir ME, Butte MJ, Freeman GJ, et al. (2008) PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. 26 :677-704

117 Butte MJ, Keir ME, Phamduy TB, et al. (2007) Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 27 (1):111-22

118 Benson DM, Bakan CE, Mishra A, et al. (2010) The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. Blood ePub Sep 2010

119 Iwai Y, Ishida M, Tanaka Y, et al. (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc. Natl. Acad. Sci. U.S.A. 99 (19):12293-7

120 Liu J, Hamrouni A, Wolowiec D, et al. (2007) Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 110 (1):296-304

121 (2014) Comprehensive molecular characterization of gastric adenocarcinoma. Nature ePub Sep 2014

122 George J, Saito M, Tsuta K, et al. (2017) Clin. Cancer Res. 23 (5):1220-1226

123 Rosell R, Carcereny E, Gervais R, et al. (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. ePub Mar 2012

124 Douillard JY, Ostoros G, Cobo M, et al. (2014) First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br. J. Cancer ePub Jan 2014

125 Sequist LV, Yang JC, Yamamoto N, et al. (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J. Clin. Oncol. ePub Sep 2013

126 Jänne PA, Yang JC, Kim DW, et al. (2015) AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N. Engl. J. Med. ePub Apr 2015

127 Pirker R, Pereira JR, von Pawel J, et al. (2012) EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. ePub Jan 2012

128 Opsomer RJ, Wese FX, Van Gangh PJ (1985) [Introduction to cerebral and spinal evoked potentials of genitourinary origin]. Acta Urol Belg 53 (1):89-95

129 Thatcher N, Hirsch FR, Luft AV, et al. (2015) Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol. ePub Jul 2015

130 Paz-Ares L, Mezger J, Ciuleanu TE, et al. (2015) Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. Lancet Oncol. ePub Mar 2015

131 Elez E, Hendlisz A, Delaunoit T, et al. (2016) Phase II study of necitumumab plus modified FOLFOX6 as first-line treatment in patients with locally advanced or metastatic colorectal cancer. Br. J. Cancer ePub Feb 2016

132 Kuenen B, Witteveen PO, Ruijter R, et al. (2010) A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. Clin. Cancer Res. 16 (6):1915-23

133 Shimamura T, Lowell AM, Engelman JA, et al. (2005) Epidermal growth factor receptors harboring kinase domain mutations associate with the heat shock protein 90 chaperone and are destabilized following exposure to geldanamycins. Cancer Res. 65 (14):6401-8

134 Shimamura T, Li D, Ji H, et al. (2008) Hsp90 inhibition suppresses mutant EGFR-T790M signaling and overcomes kinase inhibitor resistance. Cancer Res. ePub Jul 2008

135 Sawai A, Chandarlapaty S, Greulich H, et al. (2008) Inhibition of Hsp90 down-regulates mutant epidermal growth factor receptor (EGFR) expression and sensitizes EGFR mutant tumors to paclitaxel. Cancer Res. ePub Jan 2008

136 Bernardes CE, Shimizu K, Canongia Lopes JN (2015) Solvent effects on the polar network of ionic liquid solutions. J Phys Condens Matter ePub May 2015

137 Xu W, Soga S, Beebe K, et al. (2007) Sensitivity of epidermal growth factor receptor and ErbB2 exon 20 insertion mutants to Hsp90 inhibition. Br. J. Cancer 97 (6):741-4

138 Strong JE, Coffey MC, Tang D, et al. (1998) The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. EMBO J. 17 (12):3351-62

139 Coffey MC, Strong JE, Forsyth PA, et al. (1998) Reovirus therapy of tumors with activated Ras pathway. Science 282 (5392):1332-4

140 Gong J, Mita MM (2014) Activated ras signaling pathways and reovirus oncolysis: an update on the mechanism of preferential reovirus replication in cancer cells. Front Oncol 4 :167

141 Forsyth P, Roldán G, George D, et al. (2008) A phase I trial of intratumoral administration of reovirus in patients with histologically confirmed recurrent malignant gliomas. Mol. Ther. ePub Mar 2008

142 Vidal L, Pandha HS, Yap TA, et al. (2008) A phase I study of intravenous oncolytic reovirus type 3 Dearing in patients with advanced cancer. Clin. Cancer Res. 14 (21):7127-37

143 Gollamudi R, Ghalib MH, Desai KK, et al. (2010) Intravenous administration of Reolysin, a live replication competent RNA virus is safe in patients with advanced solid tumors. Invest New Drugs ePub Oct 2010

144 Harrington KJ, Karapanagiotou EM, Roulstone V, et al. (2010) Two-stage phase I dose-escalation study of intratumoral reovirus type 3 dearing and palliative radiotherapy in patients with advanced cancers. Clin. Cancer Res. 16 (11):3067-77

145 Comins C, Spicer J, Protheroe A, et al. (2010) REO-10: a phase I study of intravenous reovirus and docetaxel in patients with advanced cancer. Clin. Cancer Res. 16 (22):5564-72

146 Lolkema MP, Arkenau HT, Harrington K, et al. (2011) A phase I study of the combination of intravenous reovirus type 3 Dearing and gemcitabine in patients with advanced cancer. Clin. Cancer Res. 17 (3):581-8

147 Galanis E, Markovic SN, Suman VJ, et al. (2012) Phase II trial of intravenous administration of Reolysin(®) (Reovirus Serotype-3-dearing Strain) in patients with metastatic melanoma. Mol. Ther. ePub Oct 2012

148 Karapanagiotou EM, Roulstone V, Twigger K, et al. (2012) Phase I/II trial of carboplatin and paclitaxel chemotherapy in combination with intravenous oncolytic reovirus in patients with advanced malignancies. Clin. Cancer Res. 18 (7):2080-9

149 Morris DG, Feng X, DiFrancesco LM, et al. (2013) REO-001: A phase I trial of percutaneous intralesional administration of reovirus type 3 dearing (Reolysin®) in patients with advanced solid tumors. Invest New Drugs ePub Jun 2013

150 Albritton et al., 2006; ASCO Abstract 9518

151 Teng HW, Wang HW, Chen WM, et al. (2011) Prevalence and prognostic influence of genomic changes of EGFR pathway markers in synovial sarcoma. J Surg Oncol ePub Jun 2011

152 Capobianco G, Pili F, Contini M, et al. (2012) Analysis of epidermal growth factor receptor (EGFR) status in endometrial stromal sarcoma. Eur. J. Gynaecol. Oncol. 33 (6):629-32

153 Cascio MJ, O'Donnell RJ, Horvai AE (2010) Epithelioid sarcoma expresses epidermal growth factor receptor but gene amplification and kinase domain mutations are rare. Mod. Pathol. ePub Apr 2010

154 Yang GZ, Li J, Jin H, et al. (2013) Is mammary not otherwise specified-type sarcoma with CD10 expression a distinct entity? A rare case report with immunohistochemical and ultrastructural study. Diagn Pathol ePub Jan 2013

155 Vermi W, Giurisato E, Lonardi S, et al. (2013) Ligand-dependent activation of EGFR in follicular dendritic cells sarcoma is sustained by local production of cognate ligands. Clin. Cancer Res. 19 (18):5027-38

156 Sato O, Wada T, Kawai A, et al. (2005) Expression of epidermal growth factor receptor, ERBB2 and KIT in adult soft tissue sarcomas: a clinicopathologic study of 281 cases. Cancer 103 (9):1881-90

157 Conti A, Espina V, Chiechi A, et al. (2014) Mapping protein signal pathway interaction in sarcoma bone metastasis: linkage between rank, metalloproteinases turnover and growth factor signaling pathways. Clin. Exp. Metastasis ePub Jan 2014

158 Ciardiello F, Tortora G (2008) EGFR antagonists in cancer treatment. N. Engl. J. Med. ePub Mar 2008

159 Liang Z, Zhang J, Zeng X, et al. (2010) Relationship between EGFR expression, copy number and mutation in lung adenocarcinomas. BMC Cancer ePub Jul 2010

160 Bhargava R, Gerald WL, Li AR, et al. (2005) EGFR gene amplification in breast cancer: correlation with epidermal growth factor receptor mRNA and protein expression and HER-2 status and absence of EGFR-activating mutations. Mod. Pathol. 18 (8):1027-33

161 Yang YL, Xu KL, Zhou Y, et al. (2012) Correlation of epidermal growth factor receptor overexpression with increased epidermal growth factor receptor gene copy number in esophageal squamous cell carcinomas. Chin. Med. J. 125 (3):450-4

162 Robert C, Long GV, Brady B, et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N. Engl. J. Med. ePub Jan 2015

163 Weber JS, D'Angelo SP, Minor D, et al. (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. ePub Apr 2015

164 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. (2015) Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N. Engl. J. Med. ePub Jul 2015

165 Postow MA, Chesney J, Pavlick AC, et al. (2015) Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N. Engl. J. Med. ePub May 2015

166 Topalian SL, Sznol M, McDermott DF, et al. (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J. Clin. Oncol. ePub Apr 2014

167 Brahmer J, Reckamp KL, Baas P, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N. Engl. J. Med. ePub Jul 2015

168 Borghaei H, Paz-Ares L, Horn L, et al. (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N. Engl. J. Med. ePub Oct 2015

169 Rizvi NA, Mazières J, Planchard D, et al. (2015) Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. ePub Mar 2015

170 Motzer RJ, Escudier B, McDermott DF, et al. (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N. Engl. J. Med. ePub Nov 2015

171 Schmid et al., 2016; ASCO Abstract 11506

172 Verstovsek S, Mesa RA, Gotlib J, et al. (2013) The clinical benefit of ruxolitinib across patient subgroups: analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. Br. J. Haematol. ePub May 2013

173 Li H, Zhou X, Ran Q, et al. (2013) Parapharyngeal liposarcoma: a case report. Diagn Pathol ePub Mar 2013

174 Twa DD, Chan FC, Ben-Neriah S, et al. (2014) Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood ePub Mar 2014

175 Shi M, Roemer MG, Chapuy B, et al. (2014) Expression of programmed cell death 1 ligand 2 (PD-L2) is a distinguishing feature of primary mediastinal (thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain. Am. J. Surg. Pathol. ePub Dec 2014

176 Flynn RL, Cox KE, Jeitany M, et al. (2015) Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors. Science ePub Jan 2015

177 Koschmann C, Calinescu AA, Nunez FJ, et al. (2016) ATRX loss promotes tumor growth and impairs nonhomologous end joining DNA repair in glioma. Sci Transl Med ePub Mar 2016

178 Kovatcheva M, Liu DD, Dickson MA, et al. (2015) MDM2 turnover and expression of ATRX determine the choice between quiescence and senescence in response to CDK4 inhibition. Oncotarget ePub Apr 2015

179 Heaphy CM, de Wilde RF, Jiao Y, et al. (2011) Altered telomeres in tumors with ATRX and DAXX mutations. Science ePub Jul 2011

180 Singhi et al., 2015; USCAP Abstract 1797

181 Jiao Y, Shi C, Edil BH, et al. (2011) DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science ePub Mar 2011

182 Fishbein L, Khare S, Wubbenhorst B, et al. (2015) Whole-exome sequencing identifies somatic ATRX mutations in pheochromocytomas and paragangliomas. Nat Commun ePub Jan 2015

183 Morosini et al., 2014; ASCO Abstract 11008

184 Cheung NK, Zhang J, Lu C, et al. (2012) Association of age at diagnosis and genetic mutations in patients with neuroblastoma. JAMA ePub Mar 2012

185 Molenaar JJ, Koster J, Zwijnenburg DA, et al. (2012) Sequencing of neuroblastoma identifies chromothripsis and defects in neuritogenesis genes. Nature ePub Feb 2012

186 Pugh TJ, Morozova O, Attiyeh EF, et al. (2013) The genetic landscape of high-risk neuroblastoma. Nat. Genet. ePub Mar 2013

187 Cheung NK, Dyer MA (2013) Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat. Rev. Cancer ePub Jun 2013

188 Marinoni I, Kurrer AS, Vassella E, et al. (2014) Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology ePub Feb 2014

189 Qadeer ZA, Harcharik S, Valle-Garcia D, et al. (2014) Decreased expression of the chromatin remodeler ATRX associates with melanoma progression. J. Invest. Dermatol. ePub Jun 2014

190 Kannan K, Inagaki A, Silber J, et al. (2012) Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. Oncotarget ePub Oct 2012

191 Haberler C, Wöhrer A (null) Clinical Neuropathology practice news 2-2014: ATRX, a new candidate biomarker in gliomas. Clin. Neuropathol. 33 (2):108-11

192 Reuss DE, Sahm F, Schrimpf D, et al. (2015) ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol. ePub Jan 2015

193 Sahm F, Reuss D, Koelsche C, et al. (2014) Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma. Acta Neuropathol. ePub Oct 2014

194 Singhi et al., 2015; USCAP Abstract 93

195 Liau JY, Tsai JH, Jeng YM, et al. (2015) Leiomyosarcoma with alternative lengthening of telomeres is associated with aggressive histologic features, loss of ATRX expression, and poor clinical outcome. Am. J. Surg. Pathol. ePub Feb 2015

196 Clynes D, Higgs DR, Gibbons RJ (2013) The chromatin remodeller ATRX: a repeat offender in human disease. Trends Biochem. Sci. 38 (9):461-6

197 Ratnakumar K, Bernstein E (2013) ATRX: the case of a peculiar chromatin remodeler. Epigenetics ePub Jan 2013

198 Lovejoy CA, Li W, Reisenweber S, et al. (2012) Loss of ATRX, genome instability, and an altered DNA damage response are hallmarks of the alternative lengthening of telomeres pathway. PLoS Genet. ePub 2012

199 Bower K, Napier CE, Cole SL, et al. (2012) Loss of wild-type ATRX expression in somatic cell hybrids segregates with activation of Alternative Lengthening of Telomeres. PLoS ONE ePub 2012

200 Nan X, Hou J, Maclean A, et al. (2007) Interaction between chromatin proteins MECP2 and ATRX is disrupted by mutations that cause inherited mental retardation. Proc. Natl. Acad. Sci. U.S.A. 104 (8):2709-14

201 Garrick D, Samara V, McDowell TL, et al. (2004) A conserved truncated isoform of the ATR-X syndrome protein lacking the SWI/SNF-homology domain. Gene 326 :23-34

202 Eustermann S, Yang JC, Law MJ, et al. (2011) Combinatorial readout of histone H3 modifications specifies localization of ATRX to heterochromatin. Nat. Struct. Mol. Biol. ePub Jun 2011

203 Gibbons RJ, Picketts DJ, Villard L, et al. (1995) Mutations in a putative global transcriptional regulator cause X-linked mental retardation with alpha-thalassemia (ATR-X syndrome). Cell 80 (6):837-45

204 Love C, Sun Z, Jima D, et al. (2012) The genetic landscape of mutations in Burkitt lymphoma. Nat. Genet. ePub Dec 2012

205 Sigoillot FD, Kotsis DH, Serre V, et al. (2005) Nuclear localization and mitogen-activated protein kinase phosphorylation of the multifunctional protein CAD. J. Biol. Chem. 280 (27):25611-20

206 Konecny GE, Winterhoff B, Kolarova T, et al. (2011) Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clin. Cancer Res. 17 (6):1591-602

207 Katsumi Y, Iehara T, Miyachi M, et al. (2011) Sensitivity of malignant rhabdoid tumor cell lines to PD 0332991 is inversely correlated with p16 expression. Biochem. Biophys. Res. Commun. ePub Sep 2011

208 Cen L, Carlson BL, Schroeder MA, et al. (2012) p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-oncology ePub Jul 2012

209 Logan JE, Mostofizadeh N, Desai AJ, et al. (2013) PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res. ePub Aug 2013

210 Elvin JA, Gay LM, Ort R, et al. (2017) Oncologist ePub 04 2017

211 Gao J, Adams RP, Swain SM (2015) Does CDKN2A loss predict palbociclib benefit? Curr Oncol 22 (6):e498-501

212 Gopalan et al., 2014; ASCO Abstract 8077

213 Peguero et al., 2016; ASCO Abstract 2528

214 Konecny et al., 2016; ASCO Abstract 5557

215 DeMichele A, Clark AS, Tan KS, et al. (2015) CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin. Cancer Res. 21 (5):995-1001

216 Finn RS, Crown JP, Lang I, et al. (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. ePub Jan 2015

217 Infante JR, Cassier PA, Gerecitano JF, et al. (2016) A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin. Cancer Res. 22 (23):5696-5705

218 Johnson DB, Dahlman KH, Knol J, et al. (2014) Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. Oncologist ePub Jun 2014

219 Van Maerken T, Rihani A, Dreidax D, et al. (2011) Functional analysis of the p53 pathway in neuroblastoma cells using the small-molecule MDM2 antagonist nutlin-3. Mol. Cancer Ther. ePub Jun 2011

220 Gamble LD, Kees UR, Tweddle DA, et al. (2012) MYCN sensitizes neuroblastoma to the MDM2-p53 antagonists Nutlin-3 and MI-63. Oncogene ePub Feb 2012

221 Endo M, Kobayashi C, Setsu N, et al. (2011) Prognostic significance of p14ARF, p15INK4b, and p16INK4a inactivation in malignant peripheral nerve sheath tumors. Clin. Cancer Res. 17 (11):3771-82

222 Obana K, Yang HW, Piao HY, et al. (2003) Aberrations of p16INK4A, p14ARF and p15INK4B genes in pediatric solid tumors. Int. J. Oncol. 23 (4):1151-7

223 Louis-Brennetot C, Coindre JM, Ferreira C, et al. (2011) The CDKN2A/CDKN2B/CDK4/CCND1 pathway is pivotal in well-differentiated and dedifferentiated liposarcoma oncogenesis: an analysis of 104 tumors. Genes Chromosomes Cancer ePub Nov 2011

224 Paulson V, Chandler G, Rakheja D, et al. (2011) High-resolution array CGH identifies common mechanisms that drive embryonal rhabdomyosarcoma pathogenesis. Genes Chromosomes Cancer ePub Jun 2011

225 Park JY, Kim KR, Nam JH (2013) Immunohistochemical analysis for therapeutic targets and prognostic markers in low-grade endometrial stromal sarcoma. Int. J. Gynecol. Cancer ePub Jan 2013

226 Kawaguchi K, Oda Y, Saito T, et al. (2003) Mechanisms of inactivation of the p16INK4a gene in leiomyosarcoma of soft tissue: decreased p16 expression correlates with promoter methylation and poor prognosis. J. Pathol. 201 (3):487-95

227 Mohseny AB, Tieken C, van der Velden PA, et al. (2010) Small deletions but not methylation underlie CDKN2A/p16 loss of expression in conventional osteosarcoma. Genes Chromosomes Cancer ePub Dec 2010

228 Quelle DE, Zindy F, Ashmun RA, et al. (1995) Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest. Cell 83 (6):993-1000

229 (2005) INK4a/ARF: a multifunctional tumor suppressor locus. Mutat. Res. 576 (1-2):22-38

230 Gazzeri S, Gouyer V, Vour'ch C, et al. (1998) Mechanisms of p16INK4A inactivation in non small-cell lung cancers. Oncogene 16 (4):497-504

231 (1999) The INK4 family of cell cycle inhibitors in cancer. Oncogene 18 (38):5311-7

232 Sherr CJ, Bertwistle D, DEN Besten W, et al. (2005) p53-Dependent and -independent functions of the Arf tumor suppressor. Cold Spring Harb. Symp. Quant. Biol. 70 :129-37

233 Ozenne P, Eymin B, Brambilla E, et al. (2010) The ARF tumor suppressor: structure, functions and status in cancer. Int. J. Cancer ePub Nov 2010

234 Ruas M, Brookes S, McDonald NQ, et al. (1999) Functional evaluation of tumour-specific variants of p16INK4a/CDKN2A: correlation with protein structure information. Oncogene 18 (39):5423-34

235 Jones R, Ruas M, Gregory F, et al. (2007) A CDKN2A mutation in familial melanoma that abrogates binding of p16INK4a to CDK4 but not CDK6. Cancer Res. 67 (19):9134-41

236 Haferkamp S, Becker TM, Scurr LL, et al. (2008) p16INK4a-induced senescence is disabled by melanoma-associated mutations. Aging Cell ePub Oct 2008

237 Huot TJ, Rowe J, Harland M, et al. (2002) Biallelic mutations in p16(INK4a) confer resistance to Ras- and Ets-induced senescence in human diploid fibroblasts. Mol. Cell. Biol. 22 (23):8135-43

238 Rizos H, Darmanian AP, Holland EA, et al. (2001) Mutations in the INK4a/ARF melanoma susceptibility locus functionally impair p14ARF. J. Biol. Chem. 276 (44):41424-34

239 Gombart AF, Yang R, Campbell MJ, et al. (1997) Inhibition of growth of human leukemia cell lines by retrovirally expressed wild-type p16INK4A. Leukemia 11 (10):1673-80

240 Yang R, Gombart AF, Serrano M, et al. (1995) Mutational effects on the p16INK4a tumor suppressor protein. Cancer Res. 55 (12):2503-6

241 Parry D, Peters G (1996) Temperature-sensitive mutants of p16CDKN2 associated with familial melanoma. Mol. Cell. Biol. 16 (7):3844-52

242 Greenblatt MS, Beaudet JG, Gump JR, et al. (2003) Detailed computational study of p53 and p16: using evolutionary sequence analysis and disease-associated mutations to predict the functional consequences of allelic variants. Oncogene 22 (8):1150-63

243 Yarbrough WG, Buckmire RA, Bessho M, et al. (1999) Biologic and biochemical analyses of p16(INK4a) mutations from primary tumors. J. Natl. Cancer Inst. 91 (18):1569-74

244 Poi MJ, Yen T, Li J, et al. (2001) Somatic INK4a-ARF locus mutations: a significant mechanism of gene inactivation in squamous cell carcinomas of the head and neck. Mol. Carcinog. 30 (1):26-36

245 Byeon IJ, Li J, Ericson K, et al. (1998) Tumor suppressor p16INK4A: determination of solution structure and analyses of its interaction with cyclin-dependent kinase 4. Mol. Cell 1 (3):421-31

246 Kannengiesser C, Brookes S, del Arroyo AG, et al. (2009) Functional, structural, and genetic evaluation of 20 CDKN2A germ line mutations identified in melanoma-prone families or patients. Hum. Mutat. ePub Apr 2009

247 Lal G, Liu L, Hogg D, et al. (2000) Patients with both pancreatic adenocarcinoma and melanoma may harbor germline CDKN2A mutations. Genes Chromosomes Cancer 27 (4):358-61

248 Koh J, Enders GH, Dynlacht BD, et al. (1995) Tumour-derived p16 alleles encoding proteins defective in cell-cycle inhibition. Nature 375 (6531):506-10

249 McKenzie HA, Fung C, Becker TM, et al. (2010) Predicting functional significance of cancer-associated p16(INK4a) mutations in CDKN2A. Hum. Mutat. ePub Jun 2010

250 Miller PJ, Duraisamy S, Newell JA, et al. (2011) Classifying variants of CDKN2A using computational and laboratory studies. Hum. Mutat. ePub Aug 2011

251 Kutscher CL, Wright WA (1977) Unconditioned taste aversion to quinine induced by injections of NaCl and LiCl: dissociation of aversion from cellular dehydration. Physiol. Behav. 18 (1):87-94

252 Scaini MC, Minervini G, Elefanti L, et al. (2014) CDKN2A unclassified variants in familial malignant melanoma: combining functional and computational approaches for their assessment. Hum. Mutat. ePub Jul 2014

253 Jenkins NC, Jung J, Liu T, et al. (2013) Familial melanoma-associated mutations in p16 uncouple its tumor-suppressor functions. J. Invest. Dermatol. ePub Apr 2013

254 Walker GJ, Gabrielli BG, Castellano M, et al. (1999) Functional reassessment of P16 variants using a transfection-based assay. Int. J. Cancer 82 (2):305-12

255 Rutter JL, Goldstein AM, Dávila MR, et al. (2003) CDKN2A point mutations D153spl(c.457G>T) and IVS2+1G>T result in aberrant splice products affecting both p16INK4a and p14ARF. Oncogene 22 (28):4444-8

256 Itahana K, Zhang Y (2008) Mitochondrial p32 is a critical mediator of ARF-induced apoptosis. Cancer Cell ePub Jun 2008

257 Zhang Y, Xiong Y (1999) Mutations in human ARF exon 2 disrupt its nucleolar localization and impair its ability to block nuclear export of MDM2 and p53. Mol. Cell 3 (5):579-91

258 Zhang Y, Xiong Y, Yarbrough WG (1998) ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell 92 (6):725-34

259 Jafri M, Wake NC, Ascher DB, et al. (2015) Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma. Cancer Discov ePub Jul 2015

260 Vasioukhin V, Bauer C, Degenstein L, et al. (2001) Hyperproliferation and defects in epithelial polarity upon conditional ablation of alpha-catenin in skin. Cell 104 (4):605-17

261 Lien WH, Klezovitch O, Fernandez TE, et al. (2006) alphaE-catenin controls cerebral cortical size by regulating the hedgehog signaling pathway. Science ePub Mar 2006

262 Hoadley KA, Yau C, Hinoue T, et al. (2018) Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. Cell ePub Apr 2018

263 Van Allen EM, Wagle N, Sucker A, et al. (2014) The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov ePub Jan 2014

264 Hansford S, Kaurah P, Li-Chang H, et al. (2015) Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol ePub Apr 2015

265 Majewski IJ, Kluijt I, Cats A, et al. (2013) An α-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer. J. Pathol. ePub Mar 2013

266 Ding L, Ellis MJ, Li S, et al. (2010) Genome remodelling in a basal-like breast cancer metastasis and xenograft. Nature ePub Apr 2010

267 Piao HL, Yuan Y, Wang M, et al. (2014) α-catenin acts as a tumour suppressor in E-cadherin-negative basal-like breast cancer by inhibiting NF-κB signalling. Nat. Cell Biol. ePub Mar 2014

268 Qian J, Chen XX, Qian W, et al. (2014) Aberrant hypermethylation of CTNNA1 gene is associated with higher IPSS risk in patients with myelodysplastic syndrome. Clin. Chem. Lab. Med. ePub Dec 2014

269 Ye Y, McDevitt MA, Guo M, et al. (2009) Progressive chromatin repression and promoter methylation of CTNNA1 associated with advanced myeloid malignancies. Cancer Res. ePub Nov 2009

270 Liu TX, Becker MW, Jelinek J, et al. (2007) Chromosome 5q deletion and epigenetic suppression of the gene encoding alpha-catenin (CTNNA1) in myeloid cell transformation. Nat. Med. 13 (1):78-83

271 Chen XX, Lin J, Qian J, et al. (2014) Methylation of CTNNA1 promoter: frequent but not an adverse prognostic factor in acute myeloid leukemia. Leuk. Res. ePub May 2014

272 Li M, Gao L, Li Z, et al. (2016) CTNNA1 hypermethylation, a frequent event in acute myeloid leukemia, is independently associated with an adverse outcome. Oncotarget ePub May 2016

273 Kobielak A, Fuchs E (2004) Alpha-catenin: at the junction of intercellular adhesion and actin dynamics. Nat. Rev. Mol. Cell Biol. 5 (8):614-25

274 Bajpai S, Feng Y, Krishnamurthy R, et al. (2009) Loss of alpha-catenin decreases the strength of single E-cadherin bonds between human cancer cells. J. Biol. Chem. ePub Jul 2009

275 Silvis MR, Kreger BT, Lien WH, et al. (2011) α-catenin is a tumor suppressor that controls cell accumulation by regulating the localization and activity of the transcriptional coactivator Yap1. Sci Signal ePub May 2011

276 Inge LJ, Rajasekaran SA, Wolle D, et al. (2008) alpha-Catenin overrides Src-dependent activation of beta-catenin oncogenic signaling. Mol. Cancer Ther. 7 (6):1386-97

277 Charmsaz et al., 2014; ASH Abstract 3720

278 Swords et al., 2014; ASH Abstract 3756

279 Ding L, Kim M, Kanchi KL, et al. (2014) Clonal architectures and driver mutations in metastatic melanomas. PLoS ONE ePub 2014

280 Ross JS, Wang K, Elkadi OR, et al. (2014) Next-generation sequencing reveals frequent consistent genomic alterations in small cell undifferentiated lung cancer. J. Clin. Pathol. ePub Sep 2014

281 Huhn S, Bevier M, Pardini B, et al. (2014) Colorectal cancer risk and patients' survival: influence of polymorphisms in genes somatically mutated in colorectal tumors. Cancer Causes Control ePub Jun 2014

282 Ding L, Getz G, Wheeler DA, et al. (2008) Somatic mutations affect key pathways in lung adenocarcinoma. Nature ePub Oct 2008

283 Day BW, Stringer BW, Al-Ejeh F, et al. (2013) EphA3 maintains tumorigenicity and is a therapeutic target in glioblastoma multiforme. Cancer Cell ePub Feb 2013

284 Xi HQ, Wu XS, Wei B, et al. (2012) Aberrant expression of EphA3 in gastric carcinoma: correlation with tumor angiogenesis and survival. J. Gastroenterol. ePub Jul 2012

285 Xi HQ, Zhao P (2011) Clinicopathological significance and prognostic value of EphA3 and CD133 expression in colorectal carcinoma. J. Clin. Pathol. ePub Jun 2011

286 Lu CY, Yang ZX, Zhou L, et al. (2013) High levels of EphA3 expression are associated with high invasive capacity and poor overall survival in hepatocellular carcinoma. Oncol. Rep. ePub Nov 2013

287 Peng J, Wang Q, Liu H, et al. (2016) EPHA3 regulates the multidrug resistance of small cell lung cancer via the PI3K/BMX/STAT3 signaling pathway. Tumour Biol. ePub Sep 2016

288 Keane N, Freeman C, Swords R, et al. (2012) EPHA3 as a novel therapeutic target in the hematological malignancies. Expert Rev Hematol ePub Jun 2012

289 Guan M, Liu L, Zhao X, et al. (2011) Copy number variations of EphA3 are associated with multiple types of hematologic malignancies. Clin Lymphoma Myeloma Leuk ePub Feb 2011

290 Janes PW, Slape CI, Farnsworth RH, et al. (2014) EphA3 biology and cancer. Growth Factors ePub Dec 2014

291 Boyd AW, Bartlett PF, Lackmann M (2014) Therapeutic targeting of EPH receptors and their ligands. Nat Rev Drug Discov ePub Jan 2014

292 (2008) Eph-ephrin bidirectional signaling in physiology and disease. Cell ePub Apr 2008

293 Gao J, Aksoy BA, Dogrusoz U, et al. (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal ePub Apr 2013

294 Lisabeth EM, Fernandez C, Pasquale EB (2012) Cancer somatic mutations disrupt functions of the EphA3 receptor tyrosine kinase through multiple mechanisms. Biochemistry ePub Feb 2012

295 Zhuang G, Song W, Amato K, et al. (2012) Effects of cancer-associated EPHA3 mutations on lung cancer. J. Natl. Cancer Inst. ePub Aug 2012

296 Balakrishnan A, Bleeker FE, Lamba S, et al. (2007) Novel somatic and germline mutations in cancer candidate genes in glioblastoma, melanoma, and pancreatic carcinoma. Cancer Res. 67 (8):3545-50

297 Schultz J, Ponting CP, Hofmann K, et al. (1997) SAM as a protein interaction domain involved in developmental regulation. Protein Sci. 6 (1):249-53

298 Smalla M, Schmieder P, Kelly M, et al. (1999) Solution structure of the receptor tyrosine kinase EphB2 SAM domain and identification of two distinct homotypic interaction sites. Protein Sci. 8 (10):1954-61

299 Hock B, Böhme B, Karn T, et al. (1998) PDZ-domain-mediated interaction of the Eph-related receptor tyrosine kinase EphB3 and the ras-binding protein AF6 depends on the kinase activity of the receptor. Proc. Natl. Acad. Sci. U.S.A. 95 (17):9779-84

300 Lahtela J, Corson LB, Hemmes A, et al. (2013) A high-content cellular senescence screen identifies candidate tumor suppressors, including EPHA3. Cell Cycle ePub Feb 2013

301 Lahtela J, Pradhan B, Närhi K, et al. (2015) The putative tumor suppressor gene EphA3 fails to demonstrate a crucial role in murine lung tumorigenesis or morphogenesis. Dis Model Mech ePub Apr 2015

302 Rios J, Puhalla S (2011) PARP inhibitors in breast cancer: BRCA and beyond. Oncology (Williston Park, N.Y.) 25 (11):1014-25

303 Jacquemont C, Simon JA, D'Andrea AD, et al. (2012) Non-specific chemical inhibition of the Fanconi anemia pathway sensitizes cancer cells to cisplatin. Mol. Cancer ePub Apr 2012

304 Kratz K, Schöpf B, Kaden S, et al. (2010) Deficiency of FANCD2-associated nuclease KIAA1018/FAN1 sensitizes cells to interstrand crosslinking agents. Cell ePub Jul 2010

305 Moldovan GL, D'Andrea AD (2009) How the fanconi anemia pathway guards the genome. Annu. Rev. Genet. ePub 2009

306 Pace P, Johnson M, Tan WM, et al. (2002) FANCE: the link between Fanconi anaemia complex assembly and activity. EMBO J. 21 (13):3414-23

307 Deakyne JS, Mazin AV (2011) Fanconi anemia: at the crossroads of DNA repair. Biochemistry Mosc. ePub Jan 2011

308 Giatromanolaki A, Koukourakis MI, Sivridis E, et al. (2006) Loss of expression and nuclear/cytoplasmic localization of the FOXP1 forkhead transcription factor are common events in early endometrial cancer: relationship with estrogen receptors and HIF-1alpha expression. Mod. Pathol. 19 (1):9-16

309 Put N, Deeren D, Michaux L, et al. (2011) FOXP1 and PAX5 are rare but recurrent translocations partners in acute lymphoblastic leukemia. Cancer Genet 204 (8):462-4

310 Ernst T, Score J, Deininger M, et al. (2011) Identification of FOXP1 and SNX2 as novel ABL1 fusion partners in acute lymphoblastic leukaemia. Br. J. Haematol. ePub Apr 2011

311 Klampfl T, Harutyunyan A, Berg T, et al. (2011) Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. Blood ePub Jul 2011

312 Milosevic JD, Puda A, Malcovati L, et al. (2012) Clinical significance of genetic aberrations in secondary acute myeloid leukemia. Am. J. Hematol. ePub Nov 2012

313 Barrans SL, Fenton JA, Banham A, et al. (2004) Strong expression of FOXP1 identifies a distinct subset of diffuse large B-cell lymphoma (DLBCL) patients with poor outcome. Blood 104 (9):2933-5

314 Wong KK, Gascoyne DM, Brown PJ, et al. (2014) Reciprocal expression of the endocytic protein HIP1R and its repressor FOXP1 predicts outcome in R-CHOP-treated diffuse large B-cell lymphoma patients. Leukemia ePub Feb 2014

315 Goatly A, Bacon CM, Nakamura S, et al. (2008) FOXP1 abnormalities in lymphoma: translocation breakpoint mapping reveals insights into deregulated transcriptional control. Mod. Pathol. ePub Jul 2008

316 Rouhigharabaei L, Finalet Ferreiro J, Tousseyn T, et al. (2014) Non-IG aberrations of FOXP1 in B-cell malignancies lead to an aberrant expression of N-truncated isoforms of FOXP1. PLoS ONE ePub 2014

317 Levine DM, Ek WE, Zhang R, et al. (2013) A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. Nat. Genet. ePub Dec 2013

318 Fox SB, Brown P, Han C, et al. (2004) Expression of the forkhead transcription factor FOXP1 is associated with estrogen receptor alpha and improved survival in primary human breast carcinomas. Clin. Cancer Res. 10 (10):3521-7

319 Rayoo M, Yan M, Takano EA, et al. (2009) Expression of the forkhead box transcription factor FOXP1 is associated with oestrogen receptor alpha, oestrogen receptor beta and improved survival in familial breast cancers. J. Clin. Pathol. ePub Oct 2009

320 Feng J, Zhang X, Zhu H, et al. (2012) High expression of FoxP1 is associated with improved survival in patients with non-small cell lung cancer. Am. J. Clin. Pathol. ePub Aug 2012

321 Koon HB, Ippolito GC, Banham AH, et al. (2007) FOXP1: a potential therapeutic target in cancer. Expert Opin. Ther. Targets ePub Jul 2007

322 Brown PJ, Ashe SL, Leich E, et al. (2008) Potentially oncogenic B-cell activation-induced smaller isoforms of FOXP1 are highly expressed in the activated B cell-like subtype of DLBCL. Blood 111 (5):2816-24

323 Deisseroth A, Kaminskas E, Grillo J, et al. (2012) U.S. Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. Clin. Cancer Res. 18 (12):3212-7

324 Verstovsek S, Kantarjian HM, Estrov Z, et al. (2012) Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. Blood ePub Aug 2012

325 Barosi G, Klersy C, Villani L, et al. (2016) JAK2(V617F) allele burden ?50% is associated with response to ruxolitinib in persons with MPN-associated myelofibrosis and splenomegaly requiring therapy. Leukemia ePub 08 2016

326 Geissler et al., 2015; EHA Abstract E1347

327 Schwaab J, Knut M, Haferlach C, et al. (2015) Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Ann. Hematol. ePub Feb 2015

328 Rumi E, Milosevic JD, Selleslag D, et al. (2015) Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene. Ann. Hematol. ePub Nov 2015

329 Rumi E, Milosevic JD, Casetti I, et al. (2013) Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J. Clin. Oncol. ePub Jun 2013

330 Lierman E, Selleslag D, Smits S, et al. (2012) Ruxolitinib inhibits transforming JAK2 fusion proteins in vitro and induces complete cytogenetic remission in t(8;9)(p22;p24)/PCM1-JAK2-positive chronic eosinophilic leukemia. Blood ePub Aug 2012

331 Chase A, Bryant C, Score J, et al. (2013) Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements. Haematologica ePub Mar 2013

332 Schinnerl D, Fortschegger K, Kauer M, et al. (2015) The role of the Janus-faced transcription factor PAX5-JAK2 in acute lymphoblastic leukemia. Blood ePub Feb 2015

333 Roberts KG, Li Y, Payne-Turner D, et al. (2014) Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N. Engl. J. Med. ePub Sep 2014

334 Doudican et al., 2015; AACR Abstract 5443

335 Hao Y, Chapuy B, Monti S, et al. (2014) Selective JAK2 inhibition specifically decreases Hodgkin lymphoma and mediastinal large B-cell lymphoma growth in vitro and in vivo. Clin. Cancer Res. 20 (10):2674-83

336 Gao SM, Chen CQ, Wang LY, et al. (2013) Histone deacetylases inhibitor sodium butyrate inhibits JAK2/STAT signaling through upregulation of SOCS1 and SOCS3 mediated by HDAC8 inhibition in myeloproliferative neoplasms. Exp. Hematol. ePub Mar 2013

337 Novotny-Diermayr V, Hart S, Goh KC, et al. (2012) The oral HDAC inhibitor pracinostat (SB939) is efficacious and synergistic with the JAK2 inhibitor pacritinib (SB1518) in preclinical models of AML. Blood Cancer J ePub May 2012

338 Xiong H, Du W, Zhang YJ, et al. (2012) Trichostatin A, a histone deacetylase inhibitor, suppresses JAK2/STAT3 signaling via inducing the promoter-associated histone acetylation of SOCS1 and SOCS3 in human colorectal cancer cells. Mol. Carcinog. ePub Feb 2012

339 Bhagwat N, Koppikar P, Keller M, et al. (2014) Improved targeting of JAK2 leads to increased therapeutic efficacy in myeloproliferative neoplasms. Blood ePub Mar 2014

340 Weigert O, Lane AA, Bird L, et al. (2012) Genetic resistance to JAK2 enzymatic inhibitors is overcome by HSP90 inhibition. J. Exp. Med. ePub Feb 2012

341 Setsu N, Kohashi K, Endo M, et al. (2013) Phosphorylation of signal transducer and activator of transcription 3 in soft tissue leiomyosarcoma is associated with a better prognosis. Int. J. Cancer ePub Jan 2013

342 Jatiani SS, Baker SJ, Silverman LR, et al. (2010) Jak/STAT pathways in cytokine signaling and myeloproliferative disorders: approaches for targeted therapies. Genes Cancer ePub Oct 2010

343 Wang L, Chang J, Varghese D, et al. (2013) A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. Nat Commun ePub 2013

344 Luo W, Chang R, Zhong J, et al. (2012) Histone demethylase JMJD2C is a coactivator for hypoxia-inducible factor 1 that is required for breast cancer progression. Proc. Natl. Acad. Sci. U.S.A. ePub Dec 2012

345 Gregory BL, Cheung VG (2014) Natural variation in the histone demethylase, KDM4C, influences expression levels of specific genes including those that affect cell growth. Genome Res. ePub Jan 2014

346 Young LC, Hendzel MJ (2013) The oncogenic potential of Jumonji D2 (JMJD2/KDM4) histone demethylase overexpression. Biochem. Cell Biol. ePub Dec 2013

347 Berry WL, Janknecht R (2013) KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells. Cancer Res. ePub May 2013

348 Cheng C, Yang HW, Shang JF, et al. (2016) Identification of a small molecule that downregulates MITF expression and mediates antimelanoma activity in vitro. Melanoma Res. ePub Apr 2016

349 Morya VK, Son M, Lee HB, et al. (2014) Design and optimization of SPR-based binding assay for evaluation and screening of MITF-E-box binding inhibitor. Mol. Biotechnol. ePub Mar 2014

350 Yokoyama S, Feige E, Poling LL, et al. (2008) Pharmacologic suppression of MITF expression via HDAC inhibitors in the melanocyte lineage. Pigment Cell Melanoma Res 21 (4):457-63

351 Johannessen CM, Johnson LA, Piccioni F, et al. (2013) A melanocyte lineage program confers resistance to MAP kinase pathway inhibition. Nature ePub Dec 2013

352 McGill GG, Haq R, Nishimura EK, et al. (2006) c-Met expression is regulated by Mitf in the melanocyte lineage. J. Biol. Chem. 281 (15):10365-73

353 Beuret L, Flori E, Denoyelle C, et al. (2007) Up-regulation of MET expression by alpha-melanocyte-stimulating hormone and MITF allows hepatocyte growth factor to protect melanocytes and melanoma cells from apoptosis. J. Biol. Chem. 282 (19):14140-7

354 Wagner AJ, Goldberg JM, Dubois SG, et al. (2012) Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: results of a multicenter phase 2 trial. Cancer ePub Dec 2012

355 Basilico C, Pennacchietti S, Vigna E, et al. (2013) Tivantinib (ARQ197) displays cytotoxic activity that is independent of its ability to bind MET. Clin. Cancer Res. 19 (9):2381-92

356 Katayama R, Aoyama A, Yamori T, et al. (2013) Cytotoxic activity of tivantinib (ARQ 197) is not due solely to c-MET inhibition. Cancer Res. ePub May 2013

357 Smith MP, Ferguson J, Arozarena I, et al. (2013) Effect of SMURF2 targeting on susceptibility to MEK inhibitors in melanoma. J. Natl. Cancer Inst. ePub Jan 2013

358 Smith MP, Brunton H, Rowling EJ, et al. (2016) Inhibiting Drivers of Non-mutational Drug Tolerance Is a Salvage Strategy for Targeted Melanoma Therapy. Cancer Cell ePub Mar 2016

359 Ugurel S, Houben R, Schrama D, et al. (2007) Microphthalmia-associated transcription factor gene amplification in metastatic melanoma is a prognostic marker for patient survival, but not a predictive marker for chemosensitivity and chemotherapy response. Clin. Cancer Res. 13 (21):6344-50

360 Vergani E, Vallacchi V, Frigerio S, et al. (2011) Identification of MET and SRC activation in melanoma cell lines showing primary resistance to PLX4032. Neoplasia ePub Dec 2011

361 Garraway LA, Widlund HR, Rubin MA, et al. (2005) Integrative genomic analyses identify MITF as a lineage survival oncogene amplified in malignant melanoma. Nature ePub Jul 2005

362 Dutton-Regester K, Aoude LG, Nancarrow DJ, et al. (2012) Identification of TFG (TRK-fused gene) as a putative metastatic melanoma tumor suppressor gene. Genes Chromosomes Cancer ePub May 2012

363 Cronin JC, Wunderlich J, Loftus SK, et al. (2009) Frequent mutations in the MITF pathway in melanoma. Pigment Cell Melanoma Res 22 (4):435-44

364 Gast A, Scherer D, Chen B, et al. (2010) Somatic alterations in the melanoma genome: a high-resolution array-based comparative genomic hybridization study. Genes Chromosomes Cancer ePub Aug 2010

365 Koyanagi K, O'Day SJ, Gonzalez R, et al. (2006) Microphthalmia transcription factor as a molecular marker for circulating tumor cell detection in blood of melanoma patients. Clin. Cancer Res. 12 (4):1137-43

366 Tirosh I, Izar B, Prakadan SM, et al. (2016) Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. Science ePub Apr 2016

367 Vachtenheim J, Ondrušová L (2015) Microphthalmia-associated transcription factor expression levels in melanoma cells contribute to cell invasion and proliferation. Exp. Dermatol. ePub Jul 2015

368 Bambury RM, Battley JE, McCarthy A, et al. (2013) Translocation renal cell carcinomas: an evolving entity and a member of the microphthalmia transcription factor-associated family of tumors. Clin Genitourin Cancer ePub Sep 2013

369 (2010) The discovery of the microphthalmia locus and its gene, Mitf. Pigment Cell Melanoma Res ePub Dec 2010

370 Carreira S, Goodall J, Aksan I, et al. (2005) Mitf cooperates with Rb1 and activates p21Cip1 expression to regulate cell cycle progression. Nature ePub Feb 2005

371 Bertolotto C, Lesueur F, Giuliano S, et al. (2011) A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. Nature ePub Oct 2011

372 Debeb BG, Cohen EN, Boley K, et al. (2012) Pre-clinical studies of Notch signaling inhibitor RO4929097 in inflammatory breast cancer cells. Breast Cancer Res. Treat. ePub Jul 2012

373 Fouladi M, Stewart CF, Olson J, et al. (2011) Phase I trial of MK-0752 in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J. Clin. Oncol. ePub Sep 2011

374 Groth C, Fortini ME (2012) Therapeutic approaches to modulating Notch signaling: current challenges and future prospects. Semin. Cell Dev. Biol. ePub Jun 2012

375 Kamstrup MR, Gjerdrum LM, Biskup E, et al. (2010) Notch1 as a potential therapeutic target in cutaneous T-cell lymphoma. Blood ePub Oct 2010

376 Kridel R, Meissner B, Rogic S, et al. (2012) Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. Blood ePub Mar 2012

377 Krop I, Demuth T, Guthrie T, et al. (2012) Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J. Clin. Oncol. ePub Jul 2012

378 Rosati E, Sabatini R, De Falco F, et al. (2013) γ-Secretase inhibitor I induces apoptosis in chronic lymphocytic leukemia cells by proteasome inhibition, endoplasmic reticulum stress increase and notch down-regulation. Int. J. Cancer ePub Apr 2013

379 Samon JB, Castillo-Martin M, Hadler M, et al. (2012) Preclinical analysis of the γ-secretase inhibitor PF-03084014 in combination with glucocorticoids in T-cell acute lymphoblastic leukemia. Mol. Cancer Ther. ePub Jul 2012

380 Knoechel B, Bhatt A, Pan L, et al. (2015) Complete hematologic response of early T-cell progenitor acute lymphoblastic leukemia to the γ-secretase inhibitor BMS-906024: genetic and epigenetic findings in an outlier case. Cold Spring Harb Mol Case Stud 1 (1):a000539

381 El-Khoueiry et al., 2018; ASCO Abstract 2515

382 Gavai AV, Quesnelle C, Norris D, et al. (2015) Discovery of Clinical Candidate BMS-906024: A Potent Pan-Notch Inhibitor for the Treatment of Leukemia and Solid Tumors. ACS Med Chem Lett 6 (5):523-7

383 Dreyling M, Morschhauser F, Bouabdallah K, et al. (2017) Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. Ann. Oncol. ePub Sep 2017

384 Palomero T, Sulis ML, Cortina M, et al. (2007) Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. Nat. Med. 13 (10):1203-10

385 Liu S, Ma X, Ai Q, et al. (2013) NOTCH1 functions as an oncogene by regulating the PTEN/PI3K/AKT pathway in clear cell renal cell carcinoma. Urol. Oncol. ePub Aug 2013

386 Jour G, Scarborough JD, Jones RL, et al. (2014) Molecular profiling of soft tissue sarcomas using next-generation sequencing: a pilot study toward precision therapeutics. Hum. Pathol. ePub Aug 2014

387 Panse G, Chrisinger JS, Leung CH, et al. (2018) Clinicopathological analysis of ATRX, DAXX and NOTCH receptor expression in angiosarcomas. Histopathology ePub Jan 2018

388 Wang NJ, Sanborn Z, Arnett KL, et al. (2011) Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc. Natl. Acad. Sci. U.S.A. ePub Oct 2011

389 Klinakis A, Lobry C, Abdel-Wahab O, et al. (2011) A novel tumour-suppressor function for the Notch pathway in myeloid leukaemia. Nature ePub May 2011

390 Penton AL, Leonard LD, Spinner NB (2012) Notch signaling in human development and disease. Semin. Cell Dev. Biol. ePub Jun 2012

391 Kopan R, Ilagan MX (2009) The canonical Notch signaling pathway: unfolding the activation mechanism. Cell ePub Apr 2009

392 Sakamoto K, Chao WS, Katsube K, et al. (2005) Distinct roles of EGF repeats for the Notch signaling system. Exp. Cell Res. 302 (2):281-91

393 Malecki MJ, Sanchez-Irizarry C, Mitchell JL, et al. (2006) Leukemia-associated mutations within the NOTCH1 heterodimerization domain fall into at least two distinct mechanistic classes. Mol. Cell. Biol. 26 (12):4642-51

394 Stoeck A, Lejnine S, Truong A, et al. (2014) Discovery of biomarkers predictive of GSI response in triple-negative breast cancer and adenoid cystic carcinoma. Cancer Discov ePub Oct 2014

395 Sulis ML, Williams O, Palomero T, et al. (2008) NOTCH1 extracellular juxtamembrane expansion mutations in T-ALL. Blood ePub Aug 2008

396 Weng AP, Ferrando AA, Lee W, et al. (2004) Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science ePub Oct 2004

397 Zhu YM, Zhao WL, Fu JF, et al. (2006) NOTCH1 mutations in T-cell acute lymphoblastic leukemia: prognostic significance and implication in multifactorial leukemogenesis. Clin. Cancer Res. 12 (10):3043-9

398 Pancewicz J, Taylor JM, Datta A, et al. (2010) Notch signaling contributes to proliferation and tumor formation of human T-cell leukemia virus type 1-associated adult T-cell leukemia. Proc. Natl. Acad. Sci. U.S.A. ePub Sep 2010

399 Kanteti R, Nallasura V, Loganathan S, et al. (2009) PAX5 is expressed in small-cell lung cancer and positively regulates c-Met transcription. Lab. Invest. ePub Mar 2009

400 Song J, Li M, Tretiakova M, et al. (2010) Expression patterns of PAX5, c-Met, and paxillin in neuroendocrine tumors of the lung. Arch. Pathol. Lab. Med. ePub Nov 2010

401 Pesek M, Kopeckova M, Benesova L, et al. (2011) Clinical significance of hypermethylation status in NSCLC: evaluation of a 30-gene panel in patients with advanced disease. Anticancer Res. ePub Dec 2011

402 Palmisano WA, Crume KP, Grimes MJ, et al. (2003) Aberrant promoter methylation of the transcription factor genes PAX5 alpha and beta in human cancers. Cancer Res. 63 (15):4620-5

403 Moelans CB, Verschuur-Maes AH, van Diest PJ (2011) Frequent promoter hypermethylation of BRCA2, CDH13, MSH6, PAX5, PAX6 and WT1 in ductal carcinoma in situ and invasive breast cancer. J. Pathol. ePub Oct 2011

404 Guerrero-Preston R, Michailidi C, Marchionni L, et al. (2014) Key tumor suppressor genes inactivated by "greater promoter" methylation and somatic mutations in head and neck cancer. Epigenetics ePub Jul 2014

405 Li X, Cheung KF, Ma X, et al. (2012) Epigenetic inactivation of paired box gene 5, a novel tumor suppressor gene, through direct upregulation of p53 is associated with prognosis in gastric cancer patients. Oncogene ePub Jul 2012

406 Deng J, Liang H, Zhang R, et al. (2014) Applicability of the methylated CpG sites of paired box 5 (PAX5) promoter for prediction the prognosis of gastric cancer. Oncotarget ePub Sep 2014

407 Baumann Kubetzko FB, Di Paolo C, Maag C, et al. (2004) The PAX5 oncogene is expressed in N-type neuroblastoma cells and increases tumorigenicity of a S-type cell line. Carcinogenesis 25 (10):1839-46

408 Dong HY, Liu W, Cohen P, et al. (2005) B-cell specific activation protein encoded by the PAX-5 gene is commonly expressed in merkel cell carcinoma and small cell carcinomas. Am. J. Surg. Pathol. 29 (5):687-92

409 Mhawech-Fauceglia P, Saxena R, Zhang S, et al. (2007) Pax-5 immunoexpression in various types of benign and malignant tumours: a high-throughput tissue microarray analysis. J. Clin. Pathol. 60 (6):709-14

410 Sica G, Vazquez MF, Altorki N, et al. (2008) PAX-5 expression in pulmonary neuroendocrine neoplasms: its usefulness in surgical and fine-needle aspiration biopsy specimens. Am. J. Clin. Pathol. 129 (4):556-62

411 Kolhe R, Reid MD, Lee JR, et al. (2013) Immunohistochemical expression of PAX5 and TdT by Merkel cell carcinoma and pulmonary small cell carcinoma: a potential diagnostic pitfall but useful discriminatory marker. Int J Clin Exp Pathol ePub 2013

412 O'Brien P, Morin P, Ouellette RJ, et al. (2011) The Pax-5 gene: a pluripotent regulator of B-cell differentiation and cancer disease. Cancer Res. ePub Dec 2011

413 Medvedovic J, Ebert A, Tagoh H, et al. (2011) Pax5: a master regulator of B cell development and leukemogenesis. Adv. Immunol. ePub 2011

414 Lohr JG, Stojanov P, Lawrence MS, et al. (2012) Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. Proc. Natl. Acad. Sci. U.S.A. ePub Mar 2012

415 Waites CL, Leal-Ortiz SA, Okerlund N, et al. (2013) Bassoon and Piccolo maintain synapse integrity by regulating protein ubiquitination and degradation. EMBO J. ePub Apr 2013

416 Riabinska A, Daheim M, Herter-Sprie GS, et al. (2013) Therapeutic targeting of a robust non-oncogene addiction to PRKDC in ATM-defective tumors. Sci Transl Med ePub Jun 2013

417 Dietlein F, Thelen L, Jokic M, et al. (2014) A functional cancer genomics screen identifies a druggable synthetic lethal interaction between MSH3 and PRKDC. Cancer Discov ePub May 2014

418 Ni X, Zhang Y, Ribas J, et al. (2011) Prostate-targeted radiosensitization via aptamer-shRNA chimeras in human tumor xenografts. J. Clin. Invest. ePub Jun 2011

419 Munck JM, Batey MA, Zhao Y, et al. (2012) Chemosensitization of cancer cells by KU-0060648, a dual inhibitor of DNA-PK and PI-3K. Mol. Cancer Ther. ePub Aug 2012

420 Bouchaert P, Guerif S, Debiais C, et al. (2012) DNA-PKcs expression predicts response to radiotherapy in prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. ePub Dec 2012

421 Beskow C, Skikuniene J, Holgersson A, et al. (2009) Radioresistant cervical cancer shows upregulation of the NHEJ proteins DNA-PKcs, Ku70 and Ku86. Br. J. Cancer ePub Sep 2009

422 Söderlund Leifler K, Queseth S, Fornander T, et al. (2010) Low expression of Ku70/80, but high expression of DNA-PKcs, predict good response to radiotherapy in early breast cancer. Int. J. Oncol. ePub Dec 2010

423 Elliott SL, Crawford C, Mulligan E, et al. (2011) Mitoxantrone in combination with an inhibitor of DNA-dependent protein kinase: a potential therapy for high risk B-cell chronic lymphocytic leukaemia. Br. J. Haematol. ePub Jan 2011

424 Cornell L, Munck JM, Alsinet C, et al. (2015) DNA-PK-A candidate driver of hepatocarcinogenesis and tissue biomarker that predicts response to treatment and survival. Clin. Cancer Res. 21 (4):925-33

425 (2012) Comprehensive genomic characterization of squamous cell lung cancers. Nature ePub Sep 2012

426 Kumar A, Coleman I, Morrissey C, et al. (2016) Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. Nat. Med. ePub Apr 2016

427 Pereira B, Chin SF, Rueda OM, et al. (2016) The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. Nat Commun ePub May 2016

428 Tamura R, Yoshihara K, Yamawaki K, et al. (2015) Novel kinase fusion transcripts found in endometrial cancer. Sci Rep ePub Dec 2015

429 Hsu FM, Zhang S, Chen BP (2012) Role of DNA-dependent protein kinase catalytic subunit in cancer development and treatment. Transl Cancer Res 1 (1):22-34

430 Goodwin JF, Knudsen KE (2014) Beyond DNA repair: DNA-PK function in cancer. Cancer Discov ePub Oct 2014

431 Tonotsuka N, Hosoi Y, Miyazaki S, et al. (2006) Heterogeneous expression of DNA-dependent protein kinase in esophageal cancer and normal epithelium. Int. J. Mol. Med. 18 (3):441-7

432 Willmore E, Elliott SL, Mainou-Fowler T, et al. (2008) DNA-dependent protein kinase is a therapeutic target and an indicator of poor prognosis in B-cell chronic lymphocytic leukemia. Clin. Cancer Res. 14 (12):3984-92

433 Goodwin JF, Kothari V, Drake JM, et al. (2015) DNA-PKcs-Mediated Transcriptional Regulation Drives Prostate Cancer Progression and Metastasis. Cancer Cell ePub Jul 2015

434 Evert M, Frau M, Tomasi ML, et al. (2013) Deregulation of DNA-dependent protein kinase catalytic subunit contributes to human hepatocarcinogenesis development and has a putative prognostic value. Br. J. Cancer ePub Nov 2013

435 Xing J, Wu X, Vaporciyan AA, et al. (2008) Prognostic significance of ataxia-telangiectasia mutated, DNA-dependent protein kinase catalytic subunit, and Ku heterodimeric regulatory complex 86-kD subunit expression in patients with nonsmall cell lung cancer. Cancer 112 (12):2756-64

436 Cimino D, Fuso L, Sfiligoi C, et al. (2008) Identification of new genes associated with breast cancer progression by gene expression analysis of predefined sets of neoplastic tissues. Int. J. Cancer ePub Sep 2008

437 Lee HS, Choe G, Park KU, et al. (2007) Altered expression of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) during gastric carcinogenesis and its clinical implications on gastric cancer. Int. J. Oncol. 31 (4):859-66

438 Abdel-Fatah T, Arora A, Agarwal D, et al. (2014) Adverse prognostic and predictive significance of low DNA-dependent protein kinase catalytic subunit (DNA-PKcs) expression in early-stage breast cancers. Breast Cancer Res. Treat. ePub Jul 2014

439 Wang X, Szabo C, Qian C, et al. (2008) Mutational analysis of thirty-two double-strand DNA break repair genes in breast and pancreatic cancers. Cancer Res. ePub Feb 2008

440 Liu KW, Feng H, Bachoo R, et al. (2011) SHP-2/PTPN11 mediates gliomagenesis driven by PDGFRA and INK4A/ARF aberrations in mice and humans. J. Clin. Invest. ePub Mar 2011

441 Feng H, Liu KW, Guo P, et al. (2012) Dynamin 2 mediates PDGFRα-SHP-2-promoted glioblastoma growth and invasion. Oncogene ePub May 2012

442 Wang S, Yu WM, Zhang W, et al. (2009) Noonan syndrome/leukemia-associated gain-of-function mutations in SHP-2 phosphatase (PTPN11) enhance cell migration and angiogenesis. J. Biol. Chem. 284 (2):913-20

443 Zhou XD, Agazie YM (2008) Inhibition of SHP2 leads to mesenchymal to epithelial transition in breast cancer cells. Cell Death Differ. 15 (6):988-96

444 Elamin et al., 2015; ASCO Abstract 11077

445 Goodwin CB, Yang Z, Yin F, et al. (2012) Genetic disruption of the PI3K regulatory subunits, p85α, p55α, and p50α, normalizes mutant PTPN11-induced hypersensitivity to GM-CSF. Haematologica ePub Jul 2012

446 Krenz M, Yutzey KE, Robbins J (2005) Noonan syndrome mutation Q79R in Shp2 increases proliferation of valve primordia mesenchymal cells via extracellular signal-regulated kinase 1/2 signaling. Circ. Res. ePub Oct 2005

447 Nakamura T, Gulick J, Pratt R, et al. (2009) Noonan syndrome is associated with enhanced pERK activity, the repression of which can prevent craniofacial malformations. Proc. Natl. Acad. Sci. U.S.A. ePub Sep 2009

448 Tajan M, Batut A, Cadoudal T, et al. (2014) LEOPARD syndrome-associated SHP2 mutation confers leanness and protection from diet-induced obesity. Proc. Natl. Acad. Sci. U.S.A. ePub Oct 2014

449 Flaherty KT, Robert C, Hersey P, et al. (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. N. Engl. J. Med. ePub Jul 2012

450 Larkin J, Ascierto PA, Dréno B, et al. (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N. Engl. J. Med. ePub Nov 2014

451 Grossmann KS, Rosário M, Birchmeier C, et al. (2010) The tyrosine phosphatase Shp2 in development and cancer. Adv. Cancer Res. ePub 2010

452 Tartaglia M, Niemeyer CM, Fragale A, et al. (2003) Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat. Genet. 34 (2):148-50

453 Bard-Chapeau EA, Li S, Ding J, et al. (2011) Ptpn11/Shp2 acts as a tumor suppressor in hepatocellular carcinogenesis. Cancer Cell ePub May 2011

454 Sturla LM, Zinn PO, Ng K, et al. (2011) Src homology domain-containing phosphatase 2 suppresses cellular senescence in glioblastoma. Br. J. Cancer ePub Oct 2011

455 Brasil AS, Pereira AC, Wanderley LT, et al. (2010) PTPN11 and KRAS gene analysis in patients with Noonan and Noonan-like syndromes. Genet Test Mol Biomarkers ePub Jun 2010

456 (2009) Malignant diseases in Noonan syndrome and related disorders. Horm. Res. ePub Dec 2009

457 Chen Y, Takita J, Hiwatari M, et al. (2006) Mutations of the PTPN11 and RAS genes in rhabdomyosarcoma and pediatric hematological malignancies. Genes Chromosomes Cancer 45 (6):583-91

458 Tartaglia M, Martinelli S, Stella L, et al. (2006) Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease. Am. J. Hum. Genet. 78 (2):279-90

459 Pierpont EI, Pierpont ME, Mendelsohn NJ, et al. (2009) Genotype differences in cognitive functioning in Noonan syndrome. Genes Brain Behav. ePub Apr 2009

460 Mathur D, Somashekar S, Navarrete C, et al. (2014) Twin infant with lymphatic dysplasia diagnosed with Noonan syndrome by molecular genetic testing. Fetal Pediatr Pathol ePub Aug 2014

461 Italiano et al., 2015; ECC Abstract 302

462 Penebre et al., 2015; EORTC Abstract C87

463 Kim KH, Kim W, Howard TP, et al. (2015) SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. Nat. Med. ePub Dec 2015

464 Jelinic P, Schlappe BA, Conlon N, et al. (2016) Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type. Mod. Pathol. ePub Jan 2016

465 Karnezis AN, Wang Y, Ramos P, et al. (2016) Dual loss of the SWI/SNF complex ATPases SMARCA4/BRG1 and SMARCA2/BRM is highly sensitive and specific for small cell carcinoma of the ovary, hypercalcaemic type. J. Pathol. ePub Feb 2016

466 Chan-Penebre E, Armstrong K, Drew A, et al. (2017) Mol. Cancer Ther. ePub May 2017

467 Kothandapani A, Gopalakrishnan K, Kahali B, et al. (2012) Downregulation of SWI/SNF chromatin remodeling factor subunits modulates cisplatin cytotoxicity. Exp. Cell Res. ePub Oct 2012

468 Otte A, Rauprich F, Hillemanns P, et al. (2014) In vitro and in vivo therapeutic approach for a small cell carcinoma of the ovary hypercalcaemic type using a SCCOHT-1 cellular model. Orphanet J Rare Dis ePub Aug 2014

469 Le Loarer F, Watson S, Pierron G, et al. (2015) SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat. Genet. ePub Oct 2015

470 Kuwamoto S, Matsushita M, Takeda K, et al. (2017) SMARCA4-deficient thoracic sarcoma: report of a case and insights into how to reach the diagnosis using limited samples and resources. Hum. Pathol. ePub 12 2017

471 Sauter JL, Graham RP, Larsen BT, et al. (2017) SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior. Mod. Pathol. ePub 10 2017

472 Li L, Fan XS, Xia QY, et al. (2014) Concurrent loss of INI1, PBRM1, and BRM expression in epithelioid sarcoma: implications for the cocontributions of multiple SWI/SNF complex members to pathogenesis. Hum. Pathol. ePub Nov 2014

473 Fukuoka J, Fujii T, Shih JH, et al. (2004) Chromatin remodeling factors and BRM/BRG1 expression as prognostic indicators in non-small cell lung cancer. Clin. Cancer Res. 10 (13):4314-24

474 Bai J, Mei P, Zhang C, et al. (2013) BRG1 is a prognostic marker and potential therapeutic target in human breast cancer. PLoS ONE ePub 2013

475 Wilson BG, Roberts CW (2011) SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer ePub Jun 2011

476 Shain AH, Pollack JR (2013) The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS ONE ePub 2013

477 Trotter KW, Fan HY, Ivey ML, et al. (2008) The HSA domain of BRG1 mediates critical interactions required for glucocorticoid receptor-dependent transcriptional activation in vivo. Mol. Cell. Biol. ePub Feb 2008

478 Shen W, Xu C, Huang W, et al. (2007) Solution structure of human Brg1 bromodomain and its specific binding to acetylated histone tails. Biochemistry 46 (8):2100-10

479 Dykhuizen EC, Hargreaves DC, Miller EL, et al. (2013) BAF complexes facilitate decatenation of DNA by topoisomerase IIα. Nature ePub May 2013

480 Stanton BZ, Hodges C, Calarco JP, et al. (2017) Smarca4 ATPase mutations disrupt direct eviction of PRC1 from chromatin. Nat. Genet. ePub Feb 2017

481 Hirai H, Arai T, Okada M, et al. (2010) MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol. Ther. ePub Apr 2010

482 Bridges KA, Hirai H, Buser CA, et al. (2011) MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clin. Cancer Res. 17 (17):5638-48

483 Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. (2011) MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. Clin. Cancer Res. 17 (9):2799-806

484 Osman AA, Monroe MM, Ortega Alves MV, et al. (2015) Wee-1 kinase inhibition overcomes cisplatin resistance associated with high-risk TP53 mutations in head and neck cancer through mitotic arrest followed by senescence. Mol. Cancer Ther. ePub Feb 2015

485 Xu L, Huang CC, Huang W, et al. (2002) Systemic tumor-targeted gene delivery by anti-transferrin receptor scFv-immunoliposomes. Mol. Cancer Ther. 1 (5):337-46

486 Xu L, Tang WH, Huang CC, et al. (2001) Systemic p53 gene therapy of cancer with immunolipoplexes targeted by anti-transferrin receptor scFv. Mol. Med. 7 (10):723-34

487 Camp ER, Wang C, Little EC, et al. (2013) Transferrin receptor targeting nanomedicine delivering wild-type p53 gene sensitizes pancreatic cancer to gemcitabine therapy. Cancer Gene Ther. ePub Apr 2013

488 Kim SS, Rait A, Kim E, et al. (2015) A tumor-targeting p53 nanodelivery system limits chemoresistance to temozolomide prolonging survival in a mouse model of glioblastoma multiforme. Nanomedicine ePub Feb 2015

489 Pirollo KF, Nemunaitis J, Leung PK, et al. (2016) Safety and Efficacy in Advanced Solid Tumors of a Targeted Nanocomplex Carrying the p53 Gene Used in Combination with Docetaxel: A Phase 1b Study. Mol. Ther. ePub Sep 2016

490 Hajdenberg et al., 2012; ASCO Abstract e15010

491 Lehmann S, Bykov VJ, Ali D, et al. (2012) Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. J. Clin. Oncol. ePub Oct 2012

492 Mohell N, Alfredsson J, Fransson Å, et al. (2015) APR-246 overcomes resistance to cisplatin and doxorubicin in ovarian cancer cells. Cell Death Dis ePub Jun 2015

493 Fransson Å, Glaessgen D, Alfredsson J, et al. (2016) Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant High-Grade Serous ovarian cancer. J Ovarian Res ePub May 2016

494 Gourley et al., 2016; ASCO Abstract 5571

495 Leijen S, van Geel RM, Pavlick AC, et al. (2016) Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J. Clin. Oncol. ePub Dec 2016

496 Oza et al., 2015; ASCO Abstract 5506

497 Leijen et al., 2015; ASCO Abstract 2507

498 Ma CX, Cai S, Li S, et al. (2012) Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. J. Clin. Invest. ePub Apr 2012

499 Pérot G, Chibon F, Montero A, et al. (2010) Constant p53 pathway inactivation in a large series of soft tissue sarcomas with complex genetics. Am. J. Pathol. ePub Oct 2010

500 Taubert H, Meye A, Würl P (1996) Prognosis is correlated with p53 mutation type for soft tissue sarcoma patients. Cancer Res. 56 (18):4134-6

501 Brown CJ, Lain S, Verma CS, et al. (2009) Awakening guardian angels: drugging the p53 pathway. Nat. Rev. Cancer ePub Dec 2009

502 Joerger AC, Fersht AR (2008) Structural biology of the tumor suppressor p53. Annu. Rev. Biochem. 77 :557-82

503 Kato S, Han SY, Liu W, et al. (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc. Natl. Acad. Sci. U.S.A. 100 (14):8424-9

504 Kamada R, Nomura T, Anderson CW, et al. (2011) Cancer-associated p53 tetramerization domain mutants: quantitative analysis reveals a low threshold for tumor suppressor inactivation. J. Biol. Chem. ePub Jan 2011

505 Bougeard G, Renaux-Petel M, Flaman JM, et al. (2015) Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J. Clin. Oncol. ePub Jul 2015

506 Sorrell AD, Espenschied CR, Culver JO, et al. (2013) Tumor protein p53 (TP53) testing and Li-Fraumeni syndrome : current status of clinical applications and future directions. Mol Diagn Ther ePub Feb 2013

507 Nichols KE, Malkin D, Garber JE, et al. (2001) Germline p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol. Biomarkers Prev. 10 (2):83-7

508 Taubert H, Meye A, Würl P (1998) Soft tissue sarcomas and p53 mutations. Mol. Med. 4 (6):365-72

509 Kleihues P, Schäuble B, zur Hausen A, et al. (1997) Tumors associated with p53 germline mutations: a synopsis of 91 families. Am. J. Pathol. 150 (1):1-13

510 Gonzalez KD, Noltner KA, Buzin CH, et al. (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J. Clin. Oncol. ePub Mar 2009

511 Lalloo F, Varley J, Ellis D, et al. (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361 (9363):1101-2

512 Wang L, Lawrence MS, Wan Y, et al. (2011) SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N. Engl. J. Med. ePub Dec 2011

513 Nikolov M, Stützer A, Mosch K, et al. (2011) Chromatin affinity purification and quantitative mass spectrometry defining the interactome of histone modification patterns. Mol. Cell Proteomics ePub Nov 2011

514 Lee MG, Wynder C, Cooch N, et al. (2005) An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. Nature ePub Sep 2005

515 Hakimi MA, Dong Y, Lane WS, et al. (2003) A candidate X-linked mental retardation gene is a component of a new family of histone deacetylase-containing complexes. J. Biol. Chem. 278 (9):7234-9

516 van der Maarel SM, Scholten IH, Huber I, et al. (1996) Cloning and characterization of DXS6673E, a candidate gene for X-linked mental retardation in Xq13.1. Hum. Mol. Genet. 5 (7):887-97

517 Smedley D, Hamoudi R, Lu YJ, et al. (1999) Cloning and mapping of members of the MYM family. Genomics 60 (2):244-7

518 Lassen et al., 2018; ESMO Abstract 4090

519 Federman et al., 2018; CTOS Abstract 3029169

520 Garon EB, Rizvi NA, Hui R, et al. (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N. Engl. J. Med. ePub May 2015

521 Herbst RS, Baas P, Kim DW, et al. (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet ePub Apr 2016

522 Ayers et al., 2016; ASCO-SITC Abstract P60

523 Diaz et al., 2016; ASCO Abstract 3003

524 Le et al., 2016; ASCO GI Abstract 195

525 Fader et al., 2016; SGO Abstract 3

526 Spigel et al., 2016; ASCO Abstract 9017

527 Tawbi et al., 2016; ASCO Abstract 11006

528 Miao et al., 2016; ASCO Abstract 11043

529 Weiss et al., 2015; AACR-NCI-EORTC Abstract A50

530 Cappuzzo F, Finocchiaro G, Grossi F, et al. (2015) Phase II study of afatinib, an irreversible ErbB family blocker, in EGFR FISH-positive non-small-cell lung cancer. J Thorac Oncol ePub Apr 2015

531 Kwak EL, Shapiro GI, Cohen SM, et al. (2013) Phase 2 trial of afatinib, an ErbB family blocker, in solid tumors genetically screened for target activation. Cancer ePub Aug 2013

532 Katakami N, Atagi S, Goto K, et al. (2013) LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J. Clin. Oncol. ePub Sep 2013

533 Marshall J, Shapiro GI, Uttenreuther-Fischer M, et al. (2013) Phase I dose-escalation study of afatinib, an ErbB family blocker, plus docetaxel in patients with advanced cancer. Future Oncol ePub Feb 2013

534 Chu et al., 2013; ASCO Abstract 2523

535 Herbst RS, Gandara DR, Hirsch FR, et al. (2015) Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. Clin. Cancer Res. 21 (7):1514-24

536 Kowanetz et al., 2016; ESMO Abstract 77P

537 Smith et al., 2016; ASCO Abstract 9028

538 Mazieres et al., 2016; ASCO Abstract 9032

539 Besse et al., 2015; ECC Abstract 16LBA

540 Spigel et al., 2015; ASCO Abstract 8028

541 Balar et al., 2016; ASCO Abstract LBA4500

542 Dreicer et al., 2016; ASCO Abstract 4515

543 Powles T, Eder JP, Fine GD, et al. (2014) MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature ePub Nov 2014

544 McDermott DF, Sosman JA, Sznol M, et al. (2016) Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J. Clin. Oncol. ePub Mar 2016

545 Adams et al., 2016; ASCO Abstract 1009

546 Bendell et al., 2016; ASCO Abstract 3502

547 Disis et al., 2016; ASCO Abstract 5533

548 Dirix et al., 2016; SABCS Abstract S1-04

549 Verschraegen et al., 2016; ASCO Abstract 9036

550 Gulley et al., 2015; ECC Abstract 3090

551 Chung et al., 2016; ASCO Abstract 4009

552 Patel et al., 2016; ESMO Abstract 777PD

553 Hassan et al., 2016; ASCO Abstract 8503

554 Larkin et al., 2016; ESMO Abstract 775PD

555 Le Tourneau et al., 2016; ASCO Abstract 4516

556 Fakhrejahani et al., 2017; ASCO GU Abstract 159

557 Rajan et al., 2016; ASCO Abstract e20106

558 Bellone S, Buza N, Choi J, et al. (2018) Exceptional Response to Pembrolizumab in a Metastatic, Chemotherapy/Radiation-Resistant Ovarian Cancer Patient Harboring a PD-L1-Genetic Rearrangement. Clin. Cancer Res. 24 (14):3282-3291

559 Topalian SL, Hodi FS, Brahmer JR, et al. (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N. Engl. J. Med. ePub Jun 2012

560 Overman MJ, McDermott R, Leach JL, et al. (2017) Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. ePub Sep 2017

561 Carbone DP, Reck M, Paz-Ares L, et al. (2017) First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N. Engl. J. Med. ePub 06 2017

562 Migden MR, Rischin D, Schmults CD, et al. (2018) PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N. Engl. J. Med. ePub 07 2018

563 Moreno et al., 2018; WCLC Abstract MA04.01

564 Falchook GS, Leidner R, Stankevich E, et al. (2016) Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. J Immunother Cancer ePub 2016

565 Jiang Z, Li C, Li F, et al. (2013) EGFR gene copy number as a prognostic marker in colorectal cancer patients treated with cetuximab or panitumumab: a systematic review and meta analysis. PLoS ONE ePub 2013

566 Ha HT, Griffith KA, Zalupski MM, et al. (2013) Phase II trial of cetuximab in patients with metastatic or locally advanced soft tissue or bone sarcoma. Am. J. Clin. Oncol. ePub Feb 2013

567 Hof H, Welzel T, Debus J (2006) Effectiveness of cetuximab/gefitinib in the therapy of a sacral chordoma. Onkologie 29 (12):572-4

568 Lindén O, Stenberg L, Kjellén E (2009) Regression of cervical spinal cord compression in a patient with chordoma following treatment with cetuximab and gefitinib. Acta Oncol ePub 2009

569 Pahl JH, Ruslan SE, Buddingh EP, et al. (2012) Anti-EGFR antibody cetuximab enhances the cytolytic activity of natural killer cells toward osteosarcoma. Clin. Cancer Res. 18 (2):432-41

570 Gvozdenovic A, Boro A, Born W, et al. (2017) A bispecific antibody targeting IGF-IR and EGFR has tumor and metastasis suppressive activity in an orthotopic xenograft osteosarcoma mouse model. Am J Cancer Res 7 (7):1435-1449

571 Zhou N, Schäfer R, Li T, et al. (2018) A primary undifferentiated pleomorphic sarcoma of the lumbosacral region harboring a LMNA-NTRK1 gene fusion with durable clinical response to crizotinib: a case report. BMC Cancer ePub Aug 2018

572 Gomes et al., 2012; COSA-IPOS Abstract 702

573 Kimbara S, Takeda K, Fukushima H, et al. (2014) A case report of epithelioid inflammatory myofibroblastic sarcoma with RANBP2-ALK fusion gene treated with the ALK inhibitor, crizotinib. Jpn. J. Clin. Oncol. ePub Sep 2014

574 Butrynski JE, D'Adamo DR, Hornick JL, et al. (2010) Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N. Engl. J. Med. ePub Oct 2010

575 Mossé YP, Lim MS, Voss SD, et al. (2013) Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol. ePub May 2013

576 Subbiah V, McMahon C, Patel S, et al. (2015) STUMP un"stumped": anti-tumor response to anaplastic lymphoma kinase (ALK) inhibitor based targeted therapy in uterine inflammatory myofibroblastic tumor with myxoid features harboring DCTN1-ALK fusion. J Hematol Oncol ePub Jun 2015

577 Felkai L, Bánusz R, Kovalszky I, et al. (2017) The Presence of ALK Alterations and Clinical Relevance of Crizotinib Treatment in Pediatric Solid Tumors. Pathol. Oncol. Res. ePub Oct 2017

578 Wu YL, Cheng Y, Zhou X, et al. (2017) Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. ePub Nov 2017

579 Mok TS, Cheng Y, Zhou X, et al. (2018) Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. J. Clin. Oncol. ePub Aug 2018

580 Necchi A, Lo Vullo S, Perrone F, et al. (2018) First-line therapy with dacomitinib, an orally available pan-HER tyrosine kinase inhibitor, for locally advanced or metastatic penile squamous cell carcinoma: results of an open-label, single-arm, single-centre, phase 2 study. BJU Int. ePub 03 2018

581 Zhu Y, Shah K (2014) Multiple lesions in receptor tyrosine kinase pathway determine glioblastoma response to pan-ERBB inhibitor PF-00299804 and PI3K/mTOR dual inhibitor PF-05212384. Cancer Biol. Ther. ePub Jun 2014

582 (1979) [Exchange of clothing of a patient]. Hokenfu Zasshi 35 (8):618-21

583 Necchi et al., 2018; ASCO Abstract 399

584 Kim HS, Kwon HJ, Jung I, et al. (2015) Phase II clinical and exploratory biomarker study of dacomitinib in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Clin. Cancer Res. 21 (3):544-52

585 Kim HS, Kim SM, Kim H, et al. (2015) Phase II clinical and exploratory biomarker study of dacomitinib in recurrent and/or metastatic esophageal squamous cell carcinoma. Oncotarget ePub Dec 2015

586 Cavalieri S, Perrone F, Miceli R, et al. (2018) Efficacy and safety of single-agent pan-human epidermal growth factor receptor (HER) inhibitor dacomitinib in locally advanced unresectable or metastatic skin squamous cell cancer. Eur. J. Cancer ePub Jul 2018

587 Oh DY, Lee KW, Cho JY, et al. (2016) Phase II trial of dacomitinib in patients with HER2-positive gastric cancer. Gastric Cancer ePub Oct 2016

588 Sepúlveda-Sánchez JM, Vaz MÁ, Balañá C, et al. (2017) Phase II trial of dacomitinib, a pan-human EGFR tyrosine kinase inhibitor, in recurrent glioblastoma patients with EGFR amplification. Neuro-oncology ePub Oct 2017

589 Segal et al., 2016; ESMO Abstract 949O

590 Lutzky et al., 2014; ASCO Abstract 3001

591 Iguchi et al., 2015; ASCO Abstract 3039

592 Karzai et al., 2017; ASCO Genitourinary Abstract 162

593 Lee et al., 2016; ASCO Abstract 3015

594 Necchi et al., 2018; AACR Abstract CT102/23

595 Hamid et al., 2016; ESMO Abstract 1050PD

596 Hong et al., 2016; ESMO 2016 Abstract 1049PD

597 Yap et al., 2016; EORTC-NCI-AACR Abstract 1LBA

598 Levy A, Massard C, Soria JC, et al. (2016) Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: Single centre subset analysis from a phase 1/2 trial. Eur. J. Cancer ePub 11 2016

599 Dahabreh IJ, Linardou H, Kosmidis P, et al. (2011) EGFR gene copy number as a predictive biomarker for patients receiving tyrosine kinase inhibitor treatment: a systematic review and meta-analysis in non-small-cell lung cancer. Ann. Oncol. ePub Mar 2011

600 Cappuzzo F, Hirsch FR, Rossi E, et al. (2005) Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J. Natl. Cancer Inst. ePub May 2005

601 Dahabreh IJ, Linardou H, Siannis F, et al. (2010) Somatic EGFR mutation and gene copy gain as predictive biomarkers for response to tyrosine kinase inhibitors in non-small cell lung cancer. Clin. Cancer Res. 16 (1):291-303

602 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. N. Engl. J. Med. ePub Jul 2005

603 Moore MJ, Goldstein D, Hamm J, et al. (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J. Clin. Oncol. ePub May 2007

604 Yamasaki F, Zhang D, Bartholomeusz C, et al. (2007) Sensitivity of breast cancer cells to erlotinib depends on cyclin-dependent kinase 2 activity. Mol. Cancer Ther. 6 (8):2168-77

605 Twelves C, Trigo JM, Jones R, et al. (2008) Erlotinib in combination with capecitabine and docetaxel in patients with metastatic breast cancer: a dose-escalation study. Eur. J. Cancer 44 (3):419-26

606 Dragovich T, McCoy S, Fenoglio-Preiser CM, et al. (2006) Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J. Clin. Oncol. ePub Oct 2006

607 Ilson DH, Kelsen D, Shah M, et al. (2011) A phase 2 trial of erlotinib in patients with previously treated squamous cell and adenocarcinoma of the esophagus. Cancer 117 (7):1409-14

608 McNamara MJ, Adelstein DJ (2012) Current developments in the management of locally advanced esophageal cancer. Curr Oncol Rep ePub Aug 2012

609 Wainberg ZA, Lin LS, DiCarlo B, et al. (2011) Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. Br. J. Cancer ePub Sep 2011

610 Iyer R, Chhatrala R, Shefter T, et al. (2013) Erlotinib and radiation therapy for elderly patients with esophageal cancer - clinical and correlative results from a prospective multicenter phase 2 trial. Oncology ePub 2013

611 Han JY, Park K, Kim SW, et al. (2012) First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J. Clin. Oncol. ePub Apr 2012

612 Maemondo M, Inoue A, Kobayashi K, et al. (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N. Engl. J. Med. ePub Jun 2010

613 Mitsudomi T, Morita S, Yatabe Y, et al. (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. ePub Feb 2010

614 Mok TS, Wu YL, Thongprasert S, et al. (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N. Engl. J. Med. ePub Sep 2009

615 Petrelli F, Borgonovo K, Cabiddu M, et al. (2012) Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer ePub Mar 2012

616 Qi WX, Fu S, Zhang Q, et al. (2015) Anti-epidermal-growth-factor-receptor agents and complete responses in the treatment of advanced non-small-cell lung cancer: a meta-analysis of 17 phase III randomized controlled trials. Curr Med Res Opin ePub Jan 2015

617 Zhao H, Fan Y, Ma S, et al. (2015) Final overall survival results from a phase III, randomized, placebo-controlled, parallel-group study of gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804). J Thorac Oncol ePub Apr 2015

618 Petty RD, Dahle-Smith A, Stevenson DAJ, et al. (2017) Gefitinib and EGFR Gene Copy Number Aberrations in Esophageal Cancer. J. Clin. Oncol. ePub Jul 2017

619 Dutton SJ, Ferry DR, Blazeby JM, et al. (2014) Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. Lancet Oncol. ePub Jul 2014

620 van Cruijsen H, Voest EE, Punt CJ, et al. (2010) Phase I evaluation of cediranib, a selective VEGFR signalling inhibitor, in combination with gefitinib in patients with advanced tumours. Eur. J. Cancer ePub Mar 2010

621 Ray-Coquard I, Le Cesne A, Whelan JS, et al. (2008) A phase II study of gefitinib for patients with advanced HER-1 expressing synovial sarcoma refractory to doxorubicin-containing regimens. Oncologist 13 (4):467-73

622 Furman WL, Navid F, Daw NC, et al. (2009) Tyrosine kinase inhibitor enhances the bioavailability of oral irinotecan in pediatric patients with refractory solid tumors. J. Clin. Oncol. ePub Sep 2009

623 Ross HJ, Blumenschein GR, Aisner J, et al. (2010) Randomized phase II multicenter trial of two schedules of lapatinib as first- or second-line monotherapy in patients with advanced or metastatic non-small cell lung cancer. Clin. Cancer Res. 16 (6):1938-49

624 Geyer CE, Forster J, Lindquist D, et al. (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N. Engl. J. Med. ePub Dec 2006

625 Cameron D, Casey M, Oliva C, et al. (2010) Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist ePub 2010

626 Bian L, Wang T, Zhang S, et al. (2013) Trastuzumab plus capecitabine vs. lapatinib plus capecitabine in patients with trastuzumab resistance and taxane-pretreated metastatic breast cancer. Tumour Biol. ePub Oct 2013

627 Baselga J, Bradbury I, Eidtmann H, et al. (2012) Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet ePub Feb 2012

628 Robidoux A, Tang G, Rastogi P, et al. (2013) Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol. ePub Nov 2013

629 Alba E, Albanell J, de la Haba J, et al. (2014) Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. Br. J. Cancer ePub Mar 2014

630 Gelmon KA, Boyle FM, Kaufman B, et al. (2015) Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31. J. Clin. Oncol. ePub May 2015

631 Verma S, Miles D, Gianni L, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. N. Engl. J. Med. ePub Nov 2012

632 Johnston S, Pippen J, Pivot X, et al. (2009) Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J. Clin. Oncol. ePub Nov 2009

633 Galsky MD, Von Hoff DD, Neubauer M, et al. (2012) Target-specific, histology-independent, randomized discontinuation study of lapatinib in patients with HER2-amplified solid tumors. Invest New Drugs ePub Apr 2012

634 Burris HA, Taylor CW, Jones SF, et al. (2009) A phase I and pharmacokinetic study of oral lapatinib administered once or twice daily in patients with solid malignancies. Clin. Cancer Res. 15 (21):6702-8

635 Chu QS, Schwartz G, de Bono J, et al. (2007) Phase I and pharmacokinetic study of lapatinib in combination with capecitabine in patients with advanced solid malignancies. J. Clin. Oncol. ePub Aug 2007

636 Chew HK, Somlo G, Mack PC, et al. (2012) Phase I study of continuous and intermittent schedules of lapatinib in combination with vinorelbine in solid tumors. Ann. Oncol. ePub Apr 2012

637 Siegel-Lakhai WS, Beijnen JH, Vervenne WL, et al. (2007) Phase I pharmacokinetic study of the safety and tolerability of lapatinib (GW572016) in combination with oxaliplatin/fluorouracil/leucovorin (FOLFOX4) in patients with solid tumors. Clin. Cancer Res. 13 (15 Pt 1):4495-502

638 Tan AR, Dowlati A, Stein MN, et al. (2014) Phase I study of weekly paclitaxel in combination with pazopanib and lapatinib in advanced solid malignancies. Br. J. Cancer ePub May 2014

639 Paoluzzi et al., 2016; ASCO Abstract 11047

640 George et al., 2016; ASCO Abstract 11007

641 Heine A, Kristiansen G, Schild HH, et al. (2016) Successful treatment of refractory leiomyosarcoma with the PD-1 inhibitor nivolumab. Ann. Oncol. ePub 09 2016

642 Vlahovic G, Meadows KL, Hatch AJ, et al. (2018) A Phase I Trial of the IGF-1R Antibody Ganitumab (AMG 479) in Combination with Everolimus (RAD001) and Panitumumab in Patients with Advanced Cancer. Oncologist ePub Jul 2018