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

PATIENT

DISEASE Colon adenocarcinoma (CRC)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Colon
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Microsatellite status - MSI-High
Tumor Mutational Burden - 38 Muts/Mb

Gene Alterations

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

BRAF V600E
PTCH1 R1308fs*64
RNF43 G659fs*41
SUFU A25fs*23
BCORL1 P1681fs*20
CREBBP I1084fs*15, I1084fs*3, H2384fs*12
GATA4 G16fs*232
KRAS wildtype
MLL2 L656fs*12, R2801*
MSH3 K383fs*32
NRAS wildtype
PMS2 D414fs*34
SETD2 T1652fs*14
SPEN A2251fs*102

2 Disease relevant genes with no reportable alterations: ***KRAS, NRAS***

15 Therapies approved in the EU
0 Therapies with Lack of Response
29 Clinical Trials

GENOMIC SIGNATURES	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	none	Nivolumab 2A
		Pembrolizumab 2A
		Atezolizumab
		Avelumab
		Cemiplimab
10 Trials *see p. 20*		Durvalumab
Tumor Mutational Burden - 38 Muts/Mb	none	Atezolizumab
		Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
10 Trials *see p. 23*		Pembrolizumab

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
BRAF - V600E	Regorafenib 2A	Binimetinib 2A
		Dabrafenib 2A
		Encorafenib 2A
		Trametinib 2A
		Cobimetinib
10 Trials *see p. 25*		Vemurafenib
PTCH1 - R1308fs*64	none	Sonidegib
6 Trials *see p. 27*		Vismodegib
RNF43 - G659fs*41	none	none
2 Trials *see p. 28*		
SUFU - A25fs*23	none	none
5 Trials *see p. 29*		

2A *NCCN category*

GENE ALTERATIONS 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 Alterations section.

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

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

GENOMIC SIGNATURE

Microsatellite status

RESULT
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[2-6], including the approved therapies nivolumab[7-8], pembrolizumab[9-10], atezolizumab, avelumab, and durvalumab[3-5] . Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-H CRC compared with MSS CRC (40% vs. 0%)[9]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with tumors with high MSI than those without[7]. An earlier case study reported that nivolumab therapy resulted in a complete response in a patient with MSI-H CRC[8]. A Phase 1b trial of atezolizumab combined with bevacizumab reported PRs for 40% (4/10) of patients with MSI-H CRC[3]. MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[11-12] and FOLFIRI[13-14]. MSI and deficient MMR are associated with lack of benefit of postsurgical fluorouracil (FU)-based adjuvant therapy[15-16] but may predict benefit from irinotecan chemotherapy[17].

FREQUENCY & PROGNOSIS

MSI-H colorectal cancers (CRCs) make up 10-15% of CRC cases[2,18-21]. Multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[18,22-28]. MSI-H CRCs are associated with certain pathologic and molecular features, including poor differentiation, right-sided and mucinous tumors, increased numbers of tumor infiltrating lymphocytes, diploidy, and a relatively high frequency of BRAF mutations[19-20,29].

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[20,30-31]. 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[19,29,32]. 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[19-20,29,31].

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
38 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[33-35] and anti-PD-1 therapies[33-36]. A large-scale retrospective analysis of immune checkpoint inhibitor efficacy in CRC reported significantly improved OS for patients with tumors harboring TMB ≥ 12 Muts/Mb compared to those with tumors with TMB < 12 Muts/Mb[33]. Another study reported that a TMB ≥ 12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[37].

FREQUENCY & PROGNOSIS

Elevated TMB has been reported in 8-25% of colorectal cancer (CRC) samples[21,38-40]. Multiple studies have reported that the majority (up to 90%) of hypermutant CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)[21,40]. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and, conversely, that 100% of tumors with low TMB harbor intact MMR[38-40]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which lead to an "ultramutated" phenotype with especially high TMB[21,40]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[21,40], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[21]. Although direct associations between TMB and prognosis of patients with CRC have not been reported, multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[18,22-28].

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[41-42] and cigarette smoke in lung cancer[10,43], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21,44-47], and microsatellite instability (MSI)[21,44,47]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[33,37].

GENE
BRAF

ALTERATION
V600E

TRANSCRIPT NUMBER
NM_004333

CODING SEQUENCE EFFECT
1799T>A

POTENTIAL TREATMENT STRATEGIES

BRAF V600 mutations activate MEK-ERK signaling and are associated with sensitivity to BRAF V600 mutant-specific inhibitors such as vemurafenib[48], dabrafenib[49], and encorafenib[50-51], multikinase inhibitors that have activity against BRAF such as regorafenib[52-53], MEK inhibitors such as trametinib[54-56], cobimetinib[57], and binimetinib[58], and ERK inhibitors[59]. A Phase 2 trial of selumetinib reported PR in 32% (8/25) of pediatric patients with BRAF-mutant pilocytic astrocytoma, including 2 with BRAF V600E and 6 with a KIAA1549-BRAF fusion[60]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs in 3/19 previously treated and 1/2 newly diagnosed patients with BRAF V600E-mutant melanoma, 3/12 patients with BRAF-mutant lung cancer (2 with V600E and 1 with L597Q), and 4/21 patients with other BRAF-mutant cancers (2 with G469A, 1 with V600E, and 1 with L485W); two patients with BRAF V600E mutations also experienced CNS response[61]. BRAF V600 mutation does not generally associate with significant clinical benefit from addition of cetuximab or panitumumab to chemotherapy[62-71]. Low response rates to cetuximab or panitumumab monotherapy, or in combination with chemotherapy, have been frequently observed among patients with BRAF V600-mutated CRC, although similarly low response rates in this patient population were also often observed to chemotherapy alone; additionally, response rates were generally lower for patients with BRAF-mutated tumors than for those whose tumors were BRAF wild-type[64,67-68,71-74]. In a limited number of patients with CRC treated with cetuximab- or panitumumab-containing chemotherapy regimens, BRAF V600E was found to be present at the time of progression[75-80], to be a mechanism of acquired[81-82] or primary[83] resistance, or to be enriched in non-responders versus responders[78]. In patients with BRAF-mutated CRC, single-agent BRAF inhibitors have shown limited clinical activity[84-87]; however, significant clinical benefit has been achieved with combinatorial approaches involving BRAF inhibitors, MEK inhibitors, and EGFR antibodies[87-94]. BRAF inhibitors can induce adverse effects such as the development of cutaneous squamous cell carcinomas (SCC), keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[48-49,95].Meta-analysis confirmed a reduced risk of developing cutaneous SCC with combined BRAF- and MEK-inhibition relative to BRAF-inhibitor monotherapy[96]. A Phase 1/2 trial of PLX8394, a next-generation BRAF inhibitor predicted to not induce paradoxical MAPK pathway activation[97-98], reported PRs in patients with BRAF V600E-mutant tumors, specifically in glioma (3/4), papillary thyroid carcinoma (1/9), colorectal cancer (1/10), and ovarian cancer (1/1)[99].

FREQUENCY & PROGNOSIS

BRAF mutations have been reported in approximately 5-19% of colorectal cancer samples[72,85,100-102]. BRAF mutations have been associated with poor prognosis and shorter survival in patients with colorectal cancer, particularly those with metastatic disease, as well as with smoking history[12,64,66,103-109]. Analysis of individual BRAF mutations in 2127 patients with advanced colorectal cancer treated with chemotherapy with or without cetuximab revealed that BRAF V600E associated with poor prognosis (HR 2.60, P=1.0e-15, with median reduction of survival being 320 days) and distinct clinicopathological features, including correlation with increased peritoneal metastases compared to BRAF wild-type tumors (24% vs. 12%, P=0.0015), while BRAF D594G inactivating mutation was not prognostic (HR 1.30, P=0.37) and had similar clinicopathologic features as BRAF wild-type tumors[110].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[111-112]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[113-114]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with V600D comprising the majority of the rest[113,115-116]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[113,117]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[48-49,116,118-126]; other mutations at this position are predicted to behave similarly.

GENE
PTCH1

ALTERATION
R1308fs*64

TRANSCRIPT NUMBER
NM_000264

CODING SEQUENCE EFFECT
3921delC

POTENTIAL TREATMENT STRATEGIES

Loss of PTCH1 function results in ligand-independent and constitutive activation of SMO and downstream Hh signaling, and may predict sensitivity to SMO inhibitors[127-130] such as vismodegib and sonidegib. Significant clinical responses to vismodegib or sonidegib have been observed in patients with basal cell carcinoma or medulloblastoma with activated Hedgehog signaling[131-134], including in patients harboring PTCH1 mutations[132-134]; in one study, PTCH1 copy number loss was significantly associated with improved progression-free survival in patients with SHH-subtype medulloblastoma[134]. The transcriptional activity of the GLI transcription factors have been shown to be dependent on the bromo and extra C-terminal (BET) bromodomain protein BRD4; preclinical studies have shown that the BET inhibitor JQ1 results in downregulation of GLI transcriptional activity[135]. Therefore, BET inhibitors may be a relevant therapeutic approach for cancers with PTCH1 loss or inactivation. BET inhibitors are in clinical trials for multiple cancer types. 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

PTCH1 mutations have been reported in 3-4% of colorectal adenocarcinoma cases[21,136-137]. PTCH1 expression has been reported to be downregulated in colorectal adenocarcinoma, particularly in the serrated subtype[138]. Although published data investigating the prognostic implications of PTCH1 alterations in CRC are limited (PubMed, Sep 2019), a preclinical study showed that low levels of PTCH1 expression were associated with higher metastatic potential in several CRC cell lines[139]. A study of colorectal adenocarcinoma precursor lesions (aberrant crypt foci, ACF) identified PTCH1 promoter methylation and reduced mRNA and protein expression in dysplastic ACF compared to non-dysplastic ACF, suggesting that PTCH1 loss of expression due to promoter methylation may be an early event in colorectal tumorigenesis[140].

FINDING SUMMARY

The PTCH1 tumor suppressor gene encodes a 12-transmembrane protein that functions as an inhibitor of Smoothened (SMO) and downstream Hedgehog (Hh) signaling[141]. PTCH1 is a receptor for Hh ligands[142] and Hh ligand binding to PTCH1 results in derepression of SMO and downstream activation GLI-family transcription factors[143]. Inactivating germline mutations in PTCH1 are associated with Basal Cell Nevus Syndrome (Gorlin syndrome)[144-145]. Patients with Gorlin syndrome develop basal cell carcinomas and are also predisposed to medulloblastoma. Somatic mutations that inactivate PTCH1 are frequently found in the sporadic forms of these cancers. Although PTCH1 truncation mutations that affect the C-terminal cytoplasmic tail, such as observed here, have been reported to repress SMO-GLI1 signaling similarly to wild-type PTCH1[146-147], the PTCH1 C-terminus may be important for signaling that is independent of the canonical Hh pathway[147-149], and it is not known if such truncation mutations predict response to SMO inhibitors.

GENE
RNF43

ALTERATION
G659fs*41

TRANSCRIPT NUMBER
NM_017763

CODING SEQUENCE EFFECT
1976delG

POTENTIAL TREATMENT STRATEGIES

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[150-154]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[155-156], 3-5% of pancreatic cancers[157], 21% of ovarian mucinous carcinomas[158], 9% of liver fluke-associated cholangiocarcinomas[159], and up to 18% of colorectal cancers[21,156]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[156], endometrial[156], and gastric cancers[160-161]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[160].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[162] that was discovered because it is overexpressed in colon cancer[163]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[150-154]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[164].

GENE
SUFU

ALTERATION
A25fs*23

TRANSCRIPT NUMBER
NM_016169

CODING SEQUENCE EFFECT
71_72insC

POTENTIAL TREATMENT STRATEGIES

Although SUFU leads to activated Hedgehog signaling[129], clinical and preclinical studies have shown that SMO inhibitors that target upstream Hedgehog signaling, such as sonidegib and vismodegib, are ineffective in cancers with alterations that inactivate SUFU[134,165]. Therapies targeting the Hh pathway downstream of SUFU are under investigation and may be appropriate for patients with SUFU mutation[129]. Arsenic trioxide has been reported to inhibit GLI transcription factors[166-168], and other Hh pathway inhibitors that act downstream of SUFU are under investigation[169-170]. The transcriptional activity of the GLI transcription factors have been shown to be dependent on the bromo and extra C-terminal (BET) bromodomain protein BRD4; preclinical studies have shown that the BET inhibitor JQ1 results in downregulation of GLI transcriptional activity in SUFU mutant cells and inhibits SUFU-mutant medulloblastoma cell growth in vitro and in vivo[135]. Therefore, BET inhibitors may be a relevant therapeutic approach for cancers with SUFU loss or inactivation. BET inhibitors are in clinical trials for multiple cancer types.

FREQUENCY & PROGNOSIS

In the TCGA Colorectal Adenocarcinoma dataset, SUFU mutation was found in 1% of cases and SUFU homozygous deletion was found in fewer than 1% of cases[21]. Increased SUFU mRNA and protein expression has been detected in colon cancer tissues, and expression correlated with tumor invasion[171].

FINDING SUMMARY

SUFU encodes a negative regulator of the Hedgehog signaling pathway that functions by sequestering and inactivating the GLI transcription factors[129]. SUFU is a tumor suppressor and germline loss-of-function mutations in SUFU are associated with pediatric medulloblastoma and meningioma[172-174]. Mice with loss of SUFU, along with p53 loss of function, develop medulloblastoma[175-176]. Alterations that disrupt the SUFU-GLI interaction[177-179], or are associated with SHH-subtype medulloblastoma[165] or childhood medulloblastoma[172,174,180], such as observed here, are predicted to result in increased GLI transcriptional activity.

GENE
BCORL1

ALTERATION
P1681fs*20

TRANSCRIPT NUMBER
NM_021946

CODING SEQUENCE EFFECT
5042delC

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address genomic alterations of BCORL1.

FREQUENCY & PROGNOSIS

Infrequent, putatively inactivating somatic mutations of BCORL1 have been observed in patients with acute myelogenous leukemia[181], suggesting a role as a tumor suppressor in this disease.

FINDING SUMMARY

BCORL1 encodes a transcriptional repressor that exhibits homology to BCOR, but unlike BCOR does not interact with BCL-6; rather, the BCoR-like 1 protein is hypothesized to function as a transcriptional corepressor through interaction with Class II histone deacetylases, CtBP, and potentially BRCA1[182-183]. BCORL1 has been implicated in transcriptional repression of E-cadherin[182].

GENE
CREBBP

ALTERATION
I1084fs*15, I1084fs*3, H2384fs*12

TRANSCRIPT NUMBER
NM_004380

CODING SEQUENCE EFFECT
- 3250delA
- 3243_3244insA
- 7150delC

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in CREBBP. The use of histone deacetylase (HDAC) inhibitors are being investigated in clinical trials that are recruiting patients with either lymphoma or urothelial carcinoma harboring CREBBP alterations. However, it has been reported that there is no correlation between CREBBP mutation status and response to HDAC inhibitors in DLBCL[184].

FREQUENCY & PROGNOSIS
CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 39%) and diffuse large B-cell lymphoma (DLBCL, 19%), and at lower frequency in acute lymphoblastic leukemia (ALL, 5%), and tumors of the urinary tract (13%), skin (9%), stomach (7%), large intestine (6%), cervix (5%), lung (5%), and endometrium (5%) (COSMIC, 2020). These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[185], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[186]. Reports have found CREBBP mutation in 62-68% of patients with FL[187-188], which was associated with immune evasion[187]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[189-190].

FINDING SUMMARY
CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[191]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[192].

GENE
GATA4

ALTERATION
G16fs*232

TRANSCRIPT NUMBER
NM_002052

CODING SEQUENCE EFFECT
45delC

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in GATA4.

FREQUENCY & PROGNOSIS
GATA4 promoter methylation and loss of expression was also reported in 67% of primary lung cancers, including 61% of squamous cell carcinomas (SCC) and 71% of adenocarcinomas[193]. Conversely, GATA4 overexpression has been associated with less favorable subtypes of neuroblastoma[194] and is associated with poor prognosis in ovarian granulosa cell tumors[195].

FINDING SUMMARY
GATA4 encodes a zinc finger transcription factor which is involved in the development of several tissues and is primarily expressed in proliferating cells in the proximal portion of the intestinal tract[196]. GATA4 expression is often lost through promoter methylation in gastric and colorectal cancer (CRC), and expression of GATA4 in CRC cell lines has been shown to block cell proliferation and migration[197].

GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES
Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[64,198-200] or panitumumab[66,201-202] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS
Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[100,203-210]. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[204-207,211-212].

FINDING SUMMARY
KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[213-214]. No alterations in KRAS were identified in this case.

GENE
MLL2

ALTERATION
L656fs*12, R2801*

TRANSCRIPT NUMBER
NM_003482

CODING SEQUENCE EFFECT
- 1966_1967insC
- 8401C>T

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS
Somatic alterations of MLL2 are frequently observed in lymphoma, including in the majority of follicular lymphomas, where the observed pattern of genomic alterations suggests a tumor suppressor function[215]. MLL2 alterations are also observed in a number of solid tumor contexts (COSMIC, 2020), being especially prevalent in squamous cell lung carcinoma[216] and small cell lung carcinoma[217].

FINDING SUMMARY
MLL2 encodes an H_3K_4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[218]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[219].

GENE
MSH3

ALTERATION
K383fs*32

TRANSCRIPT NUMBER
NM_002439

CODING SEQUENCE EFFECT
1148delA

POTENTIAL TREATMENT STRATEGIES
There are no targeted approaches to address MSH_3 mutation or loss. However, preclinical studies in the context of MSH_3-deficient cancer cells have demonstrated antitumor efficacy of DNA-PKcs inhibitors[220] and PARP inhibitors such as olaparib[221] and have shown increased chemosensitivity to cisplatin, oxaliplatin, and SN-38[221-222]. However, these remain to be tested clinically.

FREQUENCY & PROGNOSIS
MSH_3 mutations have been reported with the highest incidence in CRC (6.6%)[21], skin cancers (5.5%)[223], stomach cancers (3.0-9.1%) (COSMIC, cBioPortal, 2020), and bladder cancers (3.9%)[224], although MSH_3 loss has been reported with the highest incidence in pancreatic cancer (4.6%)[225], ovarian serous cystadenocarcinoma (4.0%) (cBioPortal, 2020), and prostate adenocarcinoma (3.6%)[226]. MSH_3 loss has been correlated with the late development and progression of a variety of sporadic cancers including lung, ovarian, bladder, breast, and colorectal tumors[227-232]. Consistent with this observation, studies have suggested that MSH_3 loss increases chromosomal instability in p53-driven tumor models[233]. Certain germline polymorphisms in MSH_3 have been associated with poor prognosis in CRC[232], HNSCC[234], non-small cell lung cancer (NSCLC)[235], and pancreatic cancer[236]. However, in one study of patients with MLH_1-deficient CRC, MSH_3 loss was associated with improved post-surgery outcome[237].

FINDING SUMMARY
MSH_3 encodes a DNA mismatch repair protein. Two MutS homolog (MSH) complexes, MSH_2-MSH_6 (MutS-alpha) and MSH_2-MSH_3 (MutS-beta), are responsible for recognition of mismatched bases[233]. MSH_3 and MutS-beta has also been shown to participate in double-strand break repair by homologous recombination[220,233]. MSH_3 loss of function has been linked to the production of tetranucleotide microsatellite frameshift mutations termed EMAST (elevated microsatellite alterations at selected tetranucleotide repeats)[238-239]. The presence of EMAST has been recognized as a biomarker in multiple solid cancers with microsatellite instability (MSI)[240]. Inactivating MSH_3 mutations found in cancer tend to be frameshift, missense, or allelic loss[232,237,241-242]. Certain germline polymorphisms in MSH_3 have been reported to increase the risk of various cancers including colorectal (CRC)[243-247], breast[243,248], esophageal[249], prostate[243,250-251], gastric[242], and head and neck squamous cell carcinoma (HNSCC)[234]. Inactivating germline polymorphisms have been associated with hereditary colorectal adenomatous polyposis[252].

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES
Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[64,198-200] or panitumumab[66,201-202] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS
The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,210,253-258]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[210] and longer survival[258-259] of patients with CRC.

FINDING SUMMARY
NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[213]. No alterations in NRAS were identified in this case.

GENE
PMS2

ALTERATION
D414fs*34

TRANSCRIPT NUMBER
NM_000535

CODING SEQUENCE EFFECT
1239delA

POTENTIAL TREATMENT STRATEGIES
Defective MMR that occurs because of mutation(s) in the MMR family, which includes MLH1, MSH2, MSH6, and PMS2, can result in microsatellite instability (MSI), which is common in colon, endometrial, and stomach cancers[30]. Alterations in PMS2 can lead to impaired MMR activity[260], and selective loss of PMS2 by either mutation or loss of expression has been reported in colorectal cancer and endometrial cancer with MSI-high phenotype[261-263]. Clinical studies have shown that MSI predicts patient responses to the anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[9,264] and nivolumab[8], and alterations resulting in PMS2 functional loss may predict sensitivity to anti-PD-1 immune checkpoint inhibitors. However, this has not been directly demonstrated. Loss of PMS2 has also been shown to sensitize p53-mutant cancer cells to certain genotoxic chemotherapeutics, including topoisomerase II inhibitors and platinum-based compounds[265].

FREQUENCY & PROGNOSIS
The lifetime risk for developing colorectal cancer for those with germline PMS2 mutations is 19% for men and 11% for women, which is considerably higher than the general population, but not as high as for mutations in other HNPCC genes such as MLH1 and MSH2 (60%)[266]. Biallelic germline PMS2 alterations have also been associated with pediatric colorectal cancer and polyposis[267]. Somatic PMS2 mutations have been reported in up to 2.4% of colorectal carcinomas[21,136]. Published data investigating the prognostic significance of PMS2 alteration in colorectal cancer are limited (PubMed, Nov 2019).

FINDING SUMMARY
PMS2 encodes an endonuclease that has been shown to play a critical role in DNA mismatch repair (MMR) and apoptotic responses to DNA damage[268]. Both abnormally high levels of PMS2, caused by protein overexpression, and inactivating mutation leading to loss of PMS2 activity have been shown to result in genomic instability, resistance to genotoxic chemotherapy, and increased tumorigenicity in vivo[269-270]. PMS2 missense mutations[260,271-273] and truncating mutations[272,274-275] have been associated with germline syndromes and the loss of MMR activity, and alterations such as seen here are predicted to be oncogenic. Germline PMS2 mutations have been associated with autosomal dominant Lynch syndrome and the rarer autosomal recessive Turcot syndrome[276-278]. Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) accounts for 1–7% of all colorectal cancers[279-280]. One study reported germline PMS2 mutation in 62% (61/99) of patients diagnosed with Lynch syndrome-associated tumors[272]. Turcot syndrome is characterized by concurring primary brain tumors and colon cancers and/or colorectal adenomas in pediatric patients[281]. Therefore, in the appropriate clinical context, germline testing of PMS2 is recommended.

GENE
SETD2

ALTERATION
T1652fs*14

TRANSCRIPT NUMBER
NM_014159

CODING SEQUENCE EFFECT
4953_4954insT

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS
Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[282]. SETD2 mutations have been detected in 6–12% of acute lymphoblastic leukemias (ALL) and reportedly increase chromosomal abnormalities and contribute to leukemia development[283-285].

FINDING SUMMARY
SETD2 encodes a histone lysine-36 methyltransferase[286] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[287]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[288].

GENE
SPEN

ALTERATION
A2251fs*102

TRANSCRIPT NUMBER
NM_015001

CODING SEQUENCE EFFECT
6750delC

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address SPEN inactivating mutations. Although gamma-secretase inhibitors are in clinical development to target NOTCH activation, it is not known if these therapies would be beneficial in the context of SPEN mutation.

FREQUENCY & PROGNOSIS
SPEN truncating mutations have been reported in adenoid cystic carcinoma (ACC) (21%)[289] and splenic marginal zone lymphoma (SMZL) (5%)[290]; NOTCH pathway gene mutations were frequent in both ACC and SMZL and observed in approximately 30% of cases[289-290].

FINDING SUMMARY
SPEN (also known as MINT or SHARP) encodes a transcriptional regulator that interacts with HDAC1 and the SMRT/NcoR corepressors[291-292]. SPEN represses the transcriptional activity of the NOTCH signaling pathway[293-294]. Activation of NOTCH signaling results in binding of the transcription factor RBPJ to the NOTCH intracellular domain and consequent activation of the NOTCH transcriptional program[295]. SPEN binding to RBPJ has been shown to repress NOTCH-mediated transcription[293-294]. SPEN alterations that result in loss of the RBPJ-interaction domain (aa 2804-2816)[293-294] or the SPOC domain (aa 3498-3664)[292] are predicted to disrupt binding of SPEN to RBPJ or corepressors and are likely to be inactivating.

Regorafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Regorafenib inhibits multiple kinases, including RET, VEGFRs, PDGFRs, KIT, and RAF-family proteins. It is available in the EU to treat patients with hepatocellular carcinoma (HCC) following sorafenib treatment and patients with unresectable metastatic gastrointestinal stromal tumors (GISTs) who have progressed on or are intolerant to imatinib and sunitinib. It is also available to treat patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies.

GENE ASSOCIATION

Alterations that activate BRAF may predict sensitivity to regorafenib. Regorafenib as a monotherapy[52-53] , or in combination with panitumumab[52], was reported to provide clinical benefit for 2 patients with BRAF V600E-mutant CRC[52-53,296] . Furthermore, a patient with an acinic cell tumor of the parotid gland harboring a duplication of the BRAF kinase domain achieved a partial response to regorafenib monotherapy, which was ongoing after 12 months of treatment[297].

SUPPORTING DATA

Regorafenib has been approved to treat patients with colorectal cancer (CRC) based on the results of a trial (Study 14387) of 753 patients with previously treated metastatic CRC, which noted an increase in progression-free survival (2.0 months vs. 1.7 months) and a significant increase in overall survival (6.4 months vs. 5.0 months) in patients treated with regorafenib compared to patients who received placebo[298]. A Phase 1 trial with regorafenib in patients with solid tumors reported antitumor activity, with 3 of 47 patients (one each with renal cell carcinoma, CRC, and osteosarcoma) achieving a partial response[299]. A Phase 1b study of regorafenib combined with nivolumab for previously treated patients with advanced CRC reported an ORR of 32% (8/25)[300]. Regorafenib use has been linked to the development of intestinal perforation in one patient with CRC and one patient with GIST[301].

Atezolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 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 available in the EU to treat patients with advanced or metastatic urothelial carcinoma following platinum-based chemotherapy or patients who are not eligible for cisplatin-containing chemotherapy and whose tumors have PD-L1 expression ≥ 5%. It is also available as a first-line treatment in combination with bevacizumab, paclitaxel, and carboplatin or in combination with nab-paclitaxel and carboplatin for patients with metastatic non-squamous NSCLC without EGFR or ALK alterations and as monotherapy to treat patients with metastatic NSCLC following chemotherapy. Patients whose tumors harbor EGFR or ALK alterations should also have received targeted therapy for these alterations. It is additionally available in combination with carboplatin and etoposide as first-line treatment for patients with extensive-stage small cell lung cancer. Atezolizumab is also available in combination with nab-paclitaxel to treat patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

GENE ASSOCIATION

On the basis of clinical data[33,37] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. 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.

SUPPORTING DATA

For patients with chemotherapy-refractory metastatic colorectal cancer (CRC), the combination of atezolizumab with the MEK inhibitor cobimetinib did not significantly increase OS (8.9 vs. 8.5 months, HR=1.00) and achieved similar PFS (HR=1.25) and ORR outcomes (2.7% vs. 2.2%) compared with regorafenib in a Phase 3 trial, which included 54% KRAS-mutated and 92% MSS or MSI-Intermediate tumors; atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[302]. A Phase 1b study also investigating cobimetinib in combination with atezolizumab reported a 8% ORR (7/84, all PRs) and median OS 9.8 months in patients with CRC; there was no association between BRAF or KRAS mutation status and response rate[303-304] . Out of 6 patients with CRC in a Phase 1 trial of atezolizumab, one patient with high PD-L1 expression on inflammatory cells experienced an objective response that was ongoing for more than 7 months[305].

Avelumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with metastatic Merkel cell carcinoma (MCC). It is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

GENE ASSOCIATION

On the basis of clinical data[33,37] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. 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.

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)[306], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[307], urothelial carcinoma[308], mesothelioma[309], ovarian carcinoma[310], and breast cancer[311], and from avelumab combined with axitinib in renal cell carcinoma[312]. 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[306,310-311] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[313-315] .

Binimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Binimetinib is a MEK inhibitor that is available in the EU in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E mutation.

GENE ASSOCIATION

On the basis of clinical evidence demonstrating the efficacy of single-agent binimetinib in patients with BRAF V600-mutant melanoma[58] and a complete response in a patient with BRAF fusion-positive ovarian cancer treated with binimetinib in combination with paclitaxel[316], BRAF activating alterations may predict sensitivity to binimetinib.

SUPPORTING DATA

A Phase 1 study evaluating single-agent binimetinib reported a 0% ORR in patients with either BRAF-mutated or KRAS-mutated CRC[317]. The combination of binimetinib with FOLFOX in patients with previously treated metastatic CRC yielded SD in 54% (7/13) of patients who received continuous dosing but 0% ORR; median PFS was reported to be 3.5 months[318]. The Phase 3 BEACON study for patients with BRAF V600E-mutated CRC showed that triplet therapy of encorafenib, MEK inhibitor binimetinib, and EGFR antibody cetuximab significantly improved median OS (9.0 vs. 5.4 months, HR=0.52) and ORR (26% vs. 2%) relative to the standard irinotecan and cetuximab therapy[88]. A combination of binimetinib, encorafenib, and CDK4/6 inhibitor ribociclib in patients with BRAF V600-mutated solid cancers elicited 1 PR and 1 SD in 3 patients with CRC[319]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[320-323], the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear[324].

Cemiplimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab 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 available in the EU to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

On the basis of clinical data[33,37], patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[8-9,325-329], MSI-H status may predict sensitivity to cemiplimab.

SUPPORTING DATA

Cemiplimab has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[330]. 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)[331-332].

Cobimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor. It is available in the EU in combination with vemurafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation.

GENE ASSOCIATION

On the basis of clinical studies of cobimetinib as a single agent[333] or in combination with other agents[57,334-335], BRAF activating mutations may predict sensitivity to MEK inhibitors such as cobimetinib. Three of four patients with BRAF-V600E-positive Erdheim-Chester disease treated with single-agent cobimetinib exhibited durable PRs and a patient with Langerhans cell histiocytosis harboring an activating BRAF mutation exhibited a CR following treatment with cobimetinib[333].

SUPPORTING DATA

Cobimetinib has been investigated primarily for the treatment of BRAF V600-mutant melanoma, and addition of cobimetinib to the BRAF inhibitor vemurafenib significantly increased PFS in this context[57]. For patients with chemotherapy-refractory metastatic colorectal cancer (CRC), the combination of cobimetinib with the anti-PD-L1 immune checkpoint inhibitor atezolizumab did not significantly increase OS (8.9 vs. 8.5 months, HR=1.00) and achieved similar PFS (HR=1.25) and ORR outcomes (2.7% vs. 2.2%) compared with regorafenib in a Phase 3 trial, which included 54% KRAS-mutated and 92% MSS or MSI-Intermediate tumors; atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[302]. A Phase 1b study also investigating cobimetinib in combination with atezolizumab reported a 8% ORR (7/84, all PRs) and median OS 9.8 months in patients with CRC; there was no association between BRAF or KRAS mutation status and response rate[303-304]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[320-323], the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear[324].

Dabrafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF inhibitor that is available in the EU either as monotherapy or in combination with trametinib to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation as well as in combination with trametinib as adjuvant treatment for completely resected advanced BRAF V600-mutated melanoma. It is also available in combination with trametinib to treat patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[48-49,116,118-125,336] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib.

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[48-49,116,118-125,336] . Clinical trials of single-agent treatment of BRAF-mutant colorectal cancers (CRCs) with BRAF inhibitors have shown a very low frequency of objective responses[85-86,337] , but combination regimens with other agents have shown improved efficacy. In patients with BRAF V600E-mutated CRC, a combination of dabrafenib and panitumumab resulted in 1 complete response (CR), 1 partial response (PR), and 16 stable disease (SD) versus 2 progressive disease (PD) outcomes, whereas a combination of dabrafenib, trametinib, and panitumumab resulted in 1 CR, 8 PR, and 20 SD versus 5 PD[338]. A clinical trial of dabrafenib combined with trametinib for 43 patients with BRAF V600E-mutant CRC reported 1 CR (2%), 4 PR (9%), and 24 SD (56%), with a median progression-free survival of 3.5 months[94]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wild-type BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutant thyroid cancer[49,95,339] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[340-344] .

Durvalumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 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 available in the EU to treat patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.

GENE ASSOCIATION

On the basis of clinical data[33,37] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. 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.

SUPPORTING DATA

In a Phase 2 trial for patients with refractory metastatic colorectal cancer (CRC), the combination of durvalumab and tremelimumab elicited a higher DCR than best supportive care (22.6% vs. 6.6%) but did not significantly increase median PFS (1.8 vs. 1.9 months) or OS (6.6 vs. 4.1 months, HR=0.72, p=0.07) in the overall population. For patients with MSS tumors (OS HR=0.66), TMB greater than 28 muts/Mb was associated with greatest OS benefit (HR=0.34, p=0.07) from durvalumab/tremelimumab.

Encorafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Encorafenib is a BRAF inhibitor that is available in the EU in combination with binimetinib to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

GENE ASSOCIATION

On the basis of clinical efficacy in patients with BRAF V600-mutated melanoma[50-51] and activity in colorectal cancer[93], alterations affecting BRAF V600 may predict sensitivity to encorafenib.

SUPPORTING DATA

As a monotherapy, encorafenib exhibited modest activity in patients with BRAF V600E-mutated CRC, with no confirmed responses, 3 unconfirmed responses, 9 additional instances of SD and 4 PD, with median PFS of 4.0 months[345]. The Phase 3 BEACON study for patients with BRAF V600E-mutated CRC showed that triplet therapy of encorafenib, MEK inhibitor binimetinib, and EGFR antibody cetuximab significantly improved median OS (9.0 vs. 5.4 months, HR=0.52) and ORR (26% vs. 2%) relative to the standard irinotecan and cetuximab therapy. Encorafenib and cetuximab doublet therapy also demonstrated significant benefit over standard therapy in this trial (median OS, 8.4 months; HR=0.60; 20% ORR)[88]. In a Phase 1 trial, the addition of the PI3K-alpha inhibitor alpelisib to the combination of encorafenib and cetuximab did not enhance activity (19% vs. 18% ORR) or efficacy (3.7 vs. 4.2 months PFS)[93]. A combination of encorafenib, MEK inhibitor binimetinib, and CDK4/6 inhibitor ribociclib in a Phase 1b trial for patients with BRAF V600-mutant cancers elicited responses in melanoma, astrocytoma, unknown carcinoma, and 1 of 3 patients with CRC; a Phase 2 study of this combination in V600-mutant melanoma reported an ORR of 52.4% (22/42), including 5 CRs, median PFS of 9.2 months, and median OS of 19.4 months[319].

Nivolumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 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 available in the EU as adjuvant treatment for patients with completely resected advanced melanoma and as monotherapy or in combination with the immunotherapy ipilimumab to treat patients with unresectable or metastatic melanoma. Nivolumab is also available 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 therapy. Nivolumab is available as a monotherapy to treat patients with chemotherapy-refractory advanced non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (ASCT) and brentuximab vedotin treatment, head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, and advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

GENE ASSOCIATION

On the basis of clinical data[33,37] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[8,329] , MSI-H status may predict sensitivity to nivolumab.

SUPPORTING DATA

A Phase 2 study of nivolumab, ipilimumab, and radiation therapy for patients with pretreated MSS metastatic colorectal cancer (CRC) reported an ORR of 10% (4/40, 1 CR) and a DCR of 25% (10/40)[103]. A patient with MMR-proficient CRC who harbored amplification of the PD-L1 and PD-L2 genes experienced clinical benefit from nivolumab[346]. The Phase 2 CheckMate 142 trial (NCT02060188) of nivolumab, alone or in combination with ipilimumab, for patients with metastatic colorectal cancer (CRC) reported a significantly higher response rate in patients with tumors with high microsatellite instability (MSI-H) than in those without[329,347] . Patients with metastatic dMMR/MSI-H CRC receiving nivolumab combined with low-dose ipilimumab in the first-line settling experienced durable clinical benefit, reporting a 60% ORR (27/45, with 3 CRs, 24 PRs, and 11 SDs), with an 84% DCR; a 12-month OS rate of 83% and 12-month PFS rate of 77% were reported, and median DOR, PFS, and OS were not reached with a median follow up of 14 months[348]. For patients with metastatic dMMR/MSI-H CRC who progressed on at least 1 previous line of treatment, nivolumab alone or combined with ipilimumab elicited ORRs of 31% (23/74, with 23 PRs) and 55% (65/119, with 4 CRs and 61 PRs), and DCRs of 69% (51/74) and 80% (95/119), respectively; responses were durable and the 12-month OS rate was 73% for nivolumab monotherapy and 85% for the combination treatment[329,347] . Biomarker analyses of nivolumab plus ipilimumab in the first line setting[348], nivolumab monotherapy after disease progression[329], and nivolumab plus ipilimumab after disease progression[347] arms showed that responses were independent of PD-L1 expression levels, BRAF/KRAS mutation status, or history of Lynch syndrome. An earlier case study reported that nivolumab monotherapy resulted in a CR for a patient with MSI-H CRC[8]. Initial results from a Phase 1b/2 study evaluating nivolumab combined with capecitabine and irinotecan for previously treated metastatic CRC and pancreatic ductal adenocarcinoma cancer reported 1 PR out of 6 evaluable patients[349].

Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
38 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 available in the EU to treat patients with unresectable or metastatic melanoma, as adjuvant treatment for completely resected advanced melanoma with lymph node involvement, classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) treatment or after BV if transplant ineligible, and for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum chemotherapy or who are not eligible for cisplatin-containing chemotherapy and whose tumors are PD-L1-positive (combined positive score of at least 10). It is also available as first-line treatment for metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (at least 50% tumor proportion score) 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, as first-line treatment in combination with carboplatin and paclitaxel or nab-paclitaxel for metastatic squamous NSCLC, and as monotherapy for PD-L1-positive (at least 1% tumor proportion score) advanced NSCLC following prior therapy. Pembrolizumab is also available to treat patients with head and neck squamous cell carcinoma (HNSCC) whose tumors are recurrent or metastatic, express high PD-L1 and have progressed on or after platinum chemotherapy, and as a first-line treatment for patients with metastatic or unresectable recurrent PD-L1-positive (combined positive score of 1 or more) disease either as a monotherapy or in combination with platinum and 5-fluorouracil (5-FU). Pembrolizumab is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[33,37] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against various MSI-H or dMMR solid tumors[9,325-328] , MSI may predict sensitivity to pembrolizumab.

SUPPORTING DATA

A Phase 2 study of pembrolizumab for CRC reported a significantly higher ORR (50% [14/28] vs. 0% [0/25]), DCR (89% [25/28] vs. 16% [4/25]), PFS (not reached vs. 2.4 months), and OS (not reached vs. 6.0 months) when comparing mismatch repair deficient (mean somatic mutation number = 1782) and proficient (mean somatic mutation number = 73) samples; this corresponded to a lower risk of disease progression or death (hazard ratio 0.135 and 0.247, respectively)[9,338]. Preliminary results from a Phase 2 study that combined adjuvant pembrolizumab with radiotherapy (RT) or ablation for pretreated metastatic CRC reported an ORR of 9% (1/11) for the RT arm and no responses in the ablation arm[350].

Sonidegib

Assay findings association

PTCH1
R1308fs*64

AREAS OF THERAPEUTIC USE

Sonidegib is a small-molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Sonidegib is available in the EU to treat advanced basal cell carcinoma (BCC) that cannot be treated with curative surgery or radiotherapy.

GENE ASSOCIATION

Alterations that inactivate PTCH1 may predict sensitivity to SMO inhibitors such as sonidegib, which has shown significant clinical activity in patients with Hh pathway-activated BCC or medulloblastoma[131,351-352] . It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Studies of sonidegib have largely focused on BCC and medulloblastoma, two diseases associated with activated Hedgehog pathway (Hh) signaling. The BOLT Phase 2 trial demonstrated objective response rates (ORR) of 47% (31/66) for patients with locally advanced BCC [3% complete responses (CR), 44% partial responses (PR)] and 15% (2/13) for patients with metastatic BCC; similar results were obtained with higher dose (800mg) sonidegib (35% and 17% ORR, respectively)[352]. In three Phase 1 studies, 4/6 adults and 2/3 pediatric patients with medulloblastoma and a high Hh gene signature experienced a response to sonidegib, whereas 0/7 adults and 0/34 pediatric patients with a non-Hh gene signature responded[131]. A Phase 1 clinical trial of sonidegib for solid tumors reported stable disease (SD) for 23% of patients (24/99), lasting > 6 months for some patients with lung adenocarcinoma, spindle cell sarcoma, and BCC; ORRs of 38% (6/16) in BCC and 33% (3/9) in medulloblastoma were reported in this study[351]. Studies of sonidegib have largely focused on BCC and medulloblastoma, two diseases associated with activated Hedgehog pathway (Hh) signaling. The BOLT Phase 2 trial demonstrated objective response rates (ORR) of 47% (31/66) for patients with locally advanced BCC [3% complete responses (CR), 44% partial responses (PR)] and 15% (2/13) for patients with metastatic BCC; similar results were obtained with higher dose (800mg) sonidegib (35% and 17% ORR, respectively)[352]. In three Phase 1 studies, 4/6 adults and 2/3 pediatric patients with medulloblastoma and a high Hh gene signature experienced a response to sonidegib, whereas 0/7 adults and 0/34 pediatric patients with a non-Hh gene signature responded[131]. A Phase 1 clinical trial of sonidegib for solid tumors reported stable disease (SD) for 23% of patients (24/99), lasting > 6 months for some patients with lung adenocarcinoma, spindle cell sarcoma, and BCC; ORRs of 38% (6/16) in BCC and 33% (3/9) in medulloblastoma were reported in this study[351]. For patients with advanced solid tumors that are refractory to standard therapy and had progressed on second-line therapy, a Phase 1 trial of sonidegib combined with paclitaxel established a safe and tolerable dose and achieved partial response in 2 ovarian and 1 breast cancer patients[353].

Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is available in the EU as monotherapy or in combination with dabrafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation as well as in combination with dabrafenib as adjuvant treatment for completely resected advanced BRAF V600-mutated melanoma. It is also available in combination with dabrafenib to treat patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

GENE ASSOCIATION

Activating BRAF alterations may predict sensitivity to MEK inhibitors such as trametinib. Significant clinical responses to trametinib have been achieved by patients with melanoma harboring BRAF V600E[55-56] , V600K[55], V600R[56], K601E[56,354] , L597V[55], L597Q[354-355] , or L597S[356] mutations, by a patient with histiocytosis harboring an activating N486_P490del alteration[126], as well as by patients with tumors harboring BRAF fusions[357-361] .

SUPPORTING DATA

Preclinical studies have reported that trametinib shows some activity in colorectal cancer (CRC) cells alone and enhances antitumor effects in cells treated with 5-fluorouracil[362-363] . In addition, preclinical investigations have shown sensitivity to trametinib in cell lines with activating KRAS mutations in codons 12, 13, and 61[364]. Phase 1 and Phase 1b studies of trametinib, alone or in combination with gemcitabine, reported some activity in several types of solid tumors[320,365] . However, Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown no responses and only 1 incidence of stable disease in 31 evaluable patients with CRC, including an expansion cohort of 24 patients with KRAS mutations[321,366] . In contrast, a trial of combination treatment with selumetinib (another MEK inhibitor) and irinotecan in patients with KRAS-mutated CRC reported confirmed partial responses (PR) in 3/31 (10%) patients, an unconfirmed PR in one patient (3%), and stable disease in 15/31 (48%) patients, improving upon historical clinical trial data of irinotecan single-agent treatment; longer progression-free survival compared to historical controls was also achieved[367]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported stable disease in 43% of patients with KRAS-mutated CRC, with responses independent of PIK3CA mutation status[368]. Another Phase 1b combination trial of trametinib and the CDK4/6 inhibitor palbociclib in solid tumors observed ongoing partial responses in 2/28 (7%) of patients, including one patient with CRC harboring a NRAS Q61K mutation[369]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[320-323] , the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear[324]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[370], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[371].

Vemurafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations. It is available in the EU to treat BRAF V600 mutation-positive unresectable or metastatic melanoma.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[48-49,116,118-125] ; therefore, this tumor may be sensitive to V600-targeted therapy such as vemurafenib.

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[48-49,116,118-125,336] . Although clinical trials of single-agent treatment of BRAF-mutated colorectal cancers (CRCs) with BRAF inhibitors have shown a very low frequency of objective responses[84-87,372] , high rates of disease control have been achieved in patients with heavily pretreated metastatic CRC with the BRAF V600 mutation treated with a combination of vemurafenib and an anti-EGFR monoclonal antibody (cetuximab or panitumumab)[87,90-92,373] . In a randomized controlled Phase 2 study for previously treated BRAF V600-mutated, RAS-wild-type, metastatic CRC, addition of vemurafenib to cetuximab and irinotecan improved median progression-free survival (PFS; 4.3 vs. 2.0 months, hazard ratio [HR] of 0.48) and response rate (16% vs. 4%); overall survival (OS) analysis showed a trend to longer median OS (9.6 vs. 5.9 months, HR of 0.73), but was limited by crossover to the vemurafenib arm[374]. Activity of this vemurafenib combination is also supported by a Phase 1b study, which reported a median PFS of 7.7 months[375]. A trial examining the efficacy of a vemurafenib plus panitumumab combination in 12 patients with CRC reported 2 partial responses (PRs), 2 stable diseases (SDs) >6 months, 4 SDs with tumor shrinkage, and 2 additional SDs; median PFS was 3.2 months and median OS was 7.6 months[92]. Of 27 patients with BRAF V600-positive CRC who received vemurafenib plus cetuximab in a Phase 2 trial, 1 (4%) exhibited a PR and 18 (69%) exhibited SD; 0 of 10 patients treated with vemurafenib alone achieved an objective response; however, 5 exhibited SD[87]. Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[48,95] . In a Phase 1b trial, patients with BRAF V600E-mutant melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[334].

Vismodegib

Assay findings association

PTCH1
R1308fs*64

AREAS OF THERAPEUTIC USE

Vismodegib is a small-molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Vismodegib is available in the EU to treat symptomatic metastatic basal cell carcinoma (BCC) and advanced BCC that cannot be treated with surgery or radiotherapy.

GENE ASSOCIATION

Based on strong clinical evidence in BCC[132] and medulloblastoma[131,133-134] , alterations that inactivate PTCH1 may predict sensitivity to vismodegib. In one study of patients with medulloblastoma treated with vismodegib, PTCH1 copy number loss was significantly associated with improved progression-free survival[134]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 trial examining the addition of vismodegib to standard therapy (FOLFOX or FOLFIRI) in colorectal cancer did not report added benefit from vismodegib, possibly due to the increased toxicity of the combination[376].

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENOMIC SIGNATURE

Microsatellite status

RESULT

MSI-High

RATIONALE

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

NCT02671435

PHASE 1/2

A Study of Durvalumab (MEDI4736) and Monalizumab in Solid Tumors

TARGETS
PD-L1, NKG2A

LOCATIONS: Arizona, Vancouver (Canada), California, Colorado, Florida, Illinois, Maryland, Massachusetts, Michigan, New Jersey, New York, Toronto (Canada), Pennsylvania, Rhode Island, Tennessee, Texas, Utah, Blacktown (Australia), Clayton (Australia), Waratah (Australia), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Leuven (Belgium), Quebec (Canada), Marseille CEDEX 5 (France), Nantes CEDEX 1 (France), Debrecen (Hungary), Milano (Italy), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Grafton (New Zealand), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Sutton (United Kingdom)

NCT03126110

PHASE 1/2

Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 Combined With Immune Therapies in Advanced or Metastatic Malignancies

TARGETS
CTLA-4, TNFRSF18, PD-1

LOCATIONS: California, Libramont (Belgium), Florida, Michigan, Missouri, New Jersey, Blacktown (Australia), Randwick (Australia), New York, North Carolina, Oklahoma, Oregon, Pennsylvania, Brisbane (Australia), Tennessee, Texas, Washington, Perth (Australia), Antwerpen (Belgium), Brussels (Belgium), Bruxelles (Belgium), Charleroi (Belgium), Ghent (Belgium), Kortrijk (Belgium), Rozzano (Italy), Barcelona (Spain), Córdoba (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Santander (Spain)

NCT03400332

PHASE 1/2

An Investigational Immuno-Therapy Study of Experimental Medication BMS-986253 Given in Combination With Nivolumab in Patients With Advanced Cancers

TARGETS
IL-8, PD-1

LOCATIONS: Edmonton (Canada), Vancouver (Canada), Colorado, Manchester (United Kingdom), Maryland, Nevada, New Jersey, New York, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Virginia, Birmingham (United Kingdom), Bruxelles (Belgium), Gent (Belgium), Napoli (Italy), Rozzano MI (Italy), Madrid (Spain), Malaga (Spain), Pamplona (Spain), Santiago Compostela (Spain), Lausanne (Switzerland), St.Gallen (Switzerland), Zuerich (Switzerland)

NCT01968109

PHASE 1/2

Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors

TARGETS
PD-1, LAG-3

LOCATIONS: Nagoya-shi (Japan), California, Colorado, Florida, Sapporo-shi (Japan), Illinois, Maryland, Massachusetts, Michigan, Minnesota, Missouri, North Sydney (Australia), New York, Toronto (Canada), Oregon, Pennsylvania, Greenslopes (Australia), Southport (Australia), Sunto-gun (Japan), Texas, Chuo-ku (Japan), Melbourne (Australia), Washington, Nedlands (Australia), Wien (Austria), Quebec (Canada), Copenhagen (Denmark), Herlev (Denmark), Helsinki (Finland), Marseille Cedex 5 (France), Nantes Cedex 01 (France), Pierre Benite Cedex (France), Toulouse Cedex 9 (France), Villejuif (France), Essen (Germany), Heilbronn (Germany), Wuerzburg (Germany), Milano (Italy), Napoli (Italy), Padova (Italy), Amsterdam (Netherlands), Oslo (Norway), Barcelona (Spain), Malaga (Spain), Pamplona (Spain), Lausanne (Switzerland), Zurich (Switzerland), London (United Kingdom), Manchester (United Kingdom)

CLINICAL TRIALS

NCT02723955

PHASE 1

Dose Escalation and Expansion Study of GSK3359609 in Subjects With Selected Advanced Solid Tumors (INDUCE-1)

TARGETS
PD-1, ICOS

LOCATIONS: California, Florida, New York, Oklahoma, Toronto (Canada), Pennsylvania, Tennessee, Siena (Italy), Heidelberg (Australia), Melbourne (Australia), Nedlands (Australia), Bordeaux Cedex (France), Lyon cedex 08 (France), Paris (France), Villejuif cedex (France), Chiba (Japan), Tokyo (Japan), Amsterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Sevilla (Spain)

NCT02817633

PHASE 1

A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
TIM-3, LAG-3, PD-1

LOCATIONS: Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Iowa, Kansas, Maryland, Massachusetts, Minnesota, New Jersey, New Mexico, New York, Ohio, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, Washington, Wisconsin, Madrid (Spain), Málaga (Spain), Pamplona (Spain)

NCT02715284

PHASE 1

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: Alabama, Calgary (Canada), Edmonton (Canada), Arizona, Arkansas, Kelowna (Canada), Vancouver (Canada), California, District of Columbia, Florida, Georgia, Illinois, Kansas, Maine, Massachusetts, Michigan, Missouri, New Mexico, New York, Lille (France), North Carolina, Ohio, Oklahoma, Hamilton (Canada), London (Canada), Oregon, Pennsylvania, Montréal (Canada), Rhode Island, Tennessee, Texas, Utah, Virginia, Washington, West Virginia, Wisconsin, Horovice (Czechia), Zlín (Czechia), Copenhagen (Denmark), Odense (Denmark), Caen (France), Marseille (France), Paris (France), Saint-Herblain (France), Villejuif (France), Milano (Italy), Napoli (Italy), Parma (Italy), Roma (Italy), Verona (Italy), Gdynia (Poland), Lublin (Poland), Olsztyn (Poland), Toruń (Poland), Barcelona (Spain), Girona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Santiago De Compostela (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Aberdeen (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Oxford (United Kingdom)

NCT04008030

PHASE 3

A Study of Nivolumab, Nivolumab Plus Ipilimumab, or Investigator's Choice Chemotherapy for the Treatment of Patients With Deficient Mismatch Repair (dMMR)/Microsatellite Instability High (MSI-H) Metastatic Colorectal Cancer (mCRC)

TARGETS
EGFR, PD-1, CTLA-4

LOCATIONS: Edmonton (Canada), Ciudad Autonoma Beunos Aires (Argentina), Chiba-shi (Japan), Kashiwa-shi (Japan), Colorado, Fukuoka-shi (Japan), Illinois, Kanazawa-city (Japan), Kawasaki-shi (Japan), Ipatinga (Brazil), Westmead (Australia), New York, Oregon, Suita-shi (Japan), Sherbrooke (Canada), Woolloongabba (Australia), Barretos (Brazil), Sao Jose De Rio Preto (Brazil), Kitaadachigun (Japan), Independencia (Chile), Elizabeth Vale (Australia), Texas, Koto-ku (Japan), Clayton (Australia), Heidelberg (Australia), Virginia, Buenos Aires (Argentina), Caba (Argentina), Viedma (Argentina), Graz (Austria), Linz (Austria), Wien (Austria), Bonheiden (Belgium), Bruxelles (Belgium), Leuven (Belgium), Sao Paulo (Brazil), Santiago (Chile), Brno (Czechia), Hradec Kralove (Czechia), Novy Jicin (Czechia), Olomouc (Czechia), Herlev (Denmark), Vejle (Denmark), Besancon Cedex (France), Marseille (France), Nantes (France), Paris (France), Pessac Cedex (France), Poitiers (France), Toulouse (France), Dresden (Germany), Essen (Germany), Hamburg (Germany), Heidelberg (Germany), Marburg (Germany), Milan (Italy), Padova (Italy), Roma (Italy), Osaka (Japan), Amsterdam (Netherlands), Utrecht (Netherlands), Bergen (Norway), Rio Piedras (Puerto Rico), Badalona-barcelona (Spain), Barcelona (Spain), Madrid (Spain), Sevilla (Spain)

NCT02983045

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) in Patients With Select Advanced or Metastatic Solid Tumors

TARGETS
PD-1, CD122, CTLA-4

LOCATIONS: Marseille (France), California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kansas, Saint-Herblain (France), Massachusetts, Michigan, Missouri, New York, Toronto (Canada), Oregon, Texas, Virginia, Washington, Edegem (Belgium), Lyon (France), Marseille Cedex 20 (France), Villejuif (France), Milano (Italy), Roma (Italy), Siena (Italy), Turin (Italy), Barcelona (Spain), Madrid (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Northwood (United Kingdom), Withington (United Kingdom)

NCT02994953

PHASE 1

A Phase Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics (PK) of Avelumab in Combination With M9241(NHS-IL12) (JAVELIN IL-12)

TARGETS
PD-L1

LOCATIONS: California, Connecticut, Florida, Louisiana, Maryland, Minnesota, Missouri, Ohio, South Carolina, Texas, Vermont, Washington, Libramont (Belgium), Wilrijk (Belgium), Bordeaux cedex (France), Dijon cedex (France), Lille cedex (France), Marseille cedex 5 (France), Pierre Benite cedex (France), Strasbourg Cedex (France), Budapest (Hungary), Milano (Italy), Padova (Italy), Siena (Italy), Amsterdam (Netherlands), Maastricht (Netherlands), Sevilla (Spain)

GENOMIC SIGNATURE
Tumor Mutational Burden

RESULT
38 Muts/Mb

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

NCT02671435

PHASE 1/2

A Study of Durvalumab (MEDI4736) and Monalizumab in Solid Tumors

TARGETS
PD-L1, NKG2A

LOCATIONS: Arizona, Vancouver (Canada), California, Colorado, Florida, Illinois, Maryland, Massachusetts, Michigan, New Jersey, New York, Toronto (Canada), Pennsylvania, Rhode Island, Tennessee, Texas, Utah, Blacktown (Australia), Clayton (Australia), Waratah (Australia), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Leuven (Belgium), Quebec (Canada), Marseille CEDEX 5 (France), Nantes CEDEX 1 (France), Debrecen (Hungary), Milano (Italy), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Grafton (New Zealand), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Sutton (United Kingdom)

NCT03126110

PHASE 1/2

Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 Combined With Immune Therapies in Advanced or Metastatic Malignancies

TARGETS
CTLA-4, TNFRSF18, PD-1

LOCATIONS: California, Libramont (Belgium), Florida, Michigan, Missouri, New Jersey, Blacktown (Australia), Randwick (Australia), New York, North Carolina, Oklahoma, Oregon, Pennsylvania, Brisbane (Australia), Tennessee, Texas, Washington, Perth (Australia), Antwerpen (Belgium), Brussels (Belgium), Bruxelles (Belgium), Charleroi (Belgium), Ghent (Belgium), Kortrijk (Belgium), Rozzano (Italy), Barcelona (Spain), Córdoba (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Santander (Spain)

NCT03400332

PHASE 1/2

An Investigational Immuno-Therapy Study of Experimental Medication BMS-986253 Given in Combination With Nivolumab in Patients With Advanced Cancers

TARGETS
IL-8, PD-1

LOCATIONS: Edmonton (Canada), Vancouver (Canada), Colorado, Manchester (United Kingdom), Maryland, Nevada, New Jersey, New York, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Virginia, Birmingham (United Kingdom), Bruxelles (Belgium), Gent (Belgium), Napoli (Italy), Rozzano MI (Italy), Madrid (Spain), Malaga (Spain), Pamplona (Spain), Santiago Compostela (Spain), Lausanne (Switzerland), St.Gallen (Switzerland), Zuerich (Switzerland)

NCT01968109

PHASE 1/2

Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors

TARGETS
PD-1, LAG-3

LOCATIONS: Nagoya-shi (Japan), California, Colorado, Florida, Sapporo-shi (Japan), Illinois, Maryland, Massachusetts, Michigan, Minnesota, Missouri, North Sydney (Australia), New York, Toronto (Canada), Oregon, Pennsylvania, Greenslopes (Australia), Southport (Australia), Sunto-gun (Japan), Texas, Chuo-ku (Japan), Melbourne (Australia), Washington, Nedlands (Australia), Wien (Austria), Quebec (Canada), Copenhagen (Denmark), Herlev (Denmark), Helsinki (Finland), Marseille Cedex 5 (France), Nantes Cedex 01 (France), Pierre Benite Cedex (France), Toulouse Cedex 9 (France), Villejuif (France), Essen (Germany), Heilbronn (Germany), Wuerzburg (Germany), Milano (Italy), Napoli (Italy), Padova (Italy), Amsterdam (Netherlands), Oslo (Norway), Barcelona (Spain), Malaga (Spain), Pamplona (Spain), Lausanne (Switzerland), Zurich (Switzerland), London (United Kingdom), Manchester (United Kingdom)

NCT02723955

PHASE 1

Dose Escalation and Expansion Study of GSK3359609 in Subjects With Selected Advanced Solid Tumors (INDUCE-1)

TARGETS
PD-1, ICOS

LOCATIONS: California, Florida, New York, Oklahoma, Toronto (Canada), Pennsylvania, Tennessee, Siena (Italy), Heidelberg (Australia), Melbourne (Australia), Nedlands (Australia), Bordeaux Cedex (France), Lyon cedex 08 (France), Paris (France), Villejuif cedex (France), Chiba (Japan), Tokyo (Japan), Amsterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Sevilla (Spain)

NCT02817633

PHASE 1

A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
TIM-3, LAG-3, PD-1

LOCATIONS: Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Iowa, Kansas, Maryland, Massachusetts, Minnesota, New Jersey, New Mexico, New York, Ohio, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, Washington, Wisconsin, Madrid (Spain), Málaga (Spain), Pamplona (Spain)

NCT02715284

PHASE 1

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: Alabama, Calgary (Canada), Edmonton (Canada), Arizona, Arkansas, Kelowna (Canada), Vancouver (Canada), California, District of Columbia, Florida, Georgia, Illinois, Kansas, Maine, Massachusetts, Michigan, Missouri, New Mexico, New York, Lille (France), North Carolina, Ohio, Oklahoma, Hamilton (Canada), London (Canada), Oregon, Pennsylvania, Montréal (Canada), Rhode Island, Tennessee, Texas, Utah, Virginia, Washington, West Virginia, Wisconsin, Horovice (Czechia), Zlín (Czechia), Copenhagen (Denmark), Odense (Denmark), Caen (France), Marseille (France), Paris (France), Saint-Herblain (France), Villejuif (France), Milano (Italy), Napoli (Italy), Parma (Italy), Roma (Italy), Verona (Italy), Gdynia (Poland), Lublin (Poland), Olsztyn (Poland), Toruń (Poland), Barcelona (Spain), Girona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Santiago De Compostela (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Aberdeen (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Oxford (United Kingdom)

NCT02983045

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) in Patients With Select Advanced or Metastatic Solid Tumors

TARGETS
PD-1, CD122, CTLA-4

LOCATIONS: Marseille (France), California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kansas, Saint-Herblain (France), Massachusetts, Michigan, Missouri, New York, Toronto (Canada), Oregon, Texas, Virginia, Washington, Edegem (Belgium), Lyon (France), Marseille Cedex 20 (France), Villejuif (France), Milano (Italy), Roma (Italy), Siena (Italy), Turin (Italy), Barcelona (Spain), Madrid (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Northwood (United Kingdom), Withington (United Kingdom)

NCT02994953

PHASE 1

A Phase Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics (PK) of Avelumab in Combination With M9241(NHS-IL12) (JAVELIN IL-12)

TARGETS
PD-L1

LOCATIONS: California, Connecticut, Florida, Louisiana, Maryland, Minnesota, Missouri, Ohio, South Carolina, Texas, Vermont, Washington, Libramont (Belgium), Wilrijk (Belgium), Bordeaux cedex (France), Dijon cedex (France), Lille cedex (France), Marseille cedex 5 (France), Pierre Benite cedex (France), Strasbourg Cedex (France), Budapest (Hungary), Milano (Italy), Padova (Italy), Siena (Italy), Amsterdam (Netherlands), Maastricht (Netherlands), Sevilla (Spain)

NCT02517398

PHASE 1

MSB0011359C (M7824) in Metastatic or Locally Advanced Solid Tumors

TARGETS
PD-L1, TGF-beta

LOCATIONS: Edmonton (Canada), Nice cedex 02 (France), Arizona, Strasbourg Cedex (France), Marseille cedex 5 (France), California, Kashiwa-shi (Japan), Cheongju-si (Korea, Republic of), Colorado, Connecticut, Dijon cedex (France), Florida, Georgia, Bordeaux cedex (France), London (United Kingdom), Manchester (United Kingdom), Seongnam-si (Korea, Republic of), Southampton (United Kingdom), Toulouse cedex 09 (France), Grenoble cedex 9 (France), Saint Herblain (France), Louisiana, Maryland, Massachusetts, Michigan, Missouri, Nevada, Blacktown (Australia), Kogarah (Australia), Liverpool (Australia), Port Macquarie (Australia), St Leonards (Australia), Waratah (Australia), Lille cedex (France), Ohio, Osakasayama-shi (Japan), Paris Cedex 10 (France), Paris cedex 12 (France), Greenslopes (Australia), Southport (Australia), Rhode Island, Lyon (France), Lyon Cedex 04 (France), Woodville South (Australia), South Carolina, Glasgow (United Kingdom), Tennessee, Texas, Candiolo (Italy), Newcastle upon Tyne (United Kingdom), East Melbourne (Australia), Malvern (Australia), Wodonga (Australia), Virginia, Washington, Murdoch (Australia), Nedlands (Australia), Bruxelles (Belgium), Charleroi (Belgium), Edegem (Belgium), Gent (Belgium), Libramont (Belgium), Liège (Belgium), Wilrijk (Belgium), Montpellier (France), Milano (Italy), Pavia (Italy), Roma (Italy), Siena (Italy), Busan (Korea, Republic of), Seoul (Korea, Republic of), Barcelona (Spain), Madrid (Spain), Sevilla (Spain), Valencia (Spain), Taipei (Taiwan)

GENE
BRAF

ALTERATION
V600E

RATIONALE
BRAF V600 mutation may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Response rates to cetuximab or panitumumab, as monotherapies or in combination with chemotherapy, have generally been found to be low for patients with BRAF V600-mutated CRC; however, improved clinical benefit has been reported from combinations of these EGFR antibodies with inhibitors of MEK or PI3K-alpha.

NCT03013491

PHASE 1/2

PROCLAIM-072: A Trial to Find Safe and Active Doses of an Investigational Drug CX-072 for Patients With Solid Tumors or Lymphomas

TARGETS
CTLA-4, PD-L1, BRAF

LOCATIONS: California, Connecticut, Illinois, Indiana, Massachusetts, Michigan, Pamplona (Spain), New York, Oregon, Tennessee, Texas, Virginia, Wisconsin, Amsterdam (Netherlands), Groningen (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Valencia (Spain), Dnepropetrovsk (Ukraine), Glasgow (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle upon Tyne (United Kingdom)

NCT03693170

PHASE 2

encorAfenib, biNimetinib and Cetuximab in Subjects witH previOusly Untreated BRAF-mutant ColoRectal Cancer

TARGETS
MEK, EGFR, BRAF

LOCATIONS: Nagoya (Japan), California, Montpellier (France), Kashiwa (Japan), Colorado, Madrid (Spain), Connecticut, Torquay (United Kingdom), Gent (Belgium), Romford (United Kingdom), Leuven (Belgium), San Giovanni Rotondo (Italy), Meldola (Italy), Fukuoka-shi (Japan), Kansas, Wiener Neustadt (Austria), Hamburg (Germany), Missouri, Pamplona (Spain), New York, Osaka-shi (Japan), Nagaizumi-cho (Japan), Sutton (United Kingdom), Tennessee, Texas, Koto-ku, (Japan), Virginia, Salzburg (Austria), Wien (Austria), Antwerp (Belgium), Brussels (Belgium), Besançon (France), Brest (France), Le Mans (France), Marseille (France), Paris (France), Pessac (France), Saint-Herblain (France), Toulouse (France), Candiolo (Italy), Genova (Italy), Perugia (Italy), Amsterdam (Netherlands), Tilburg (Netherlands), Utrecht (Netherlands), Barcelona (Spain), Toledo (Spain), Valencia (Spain), Vigo (Spain), Zaragoza (Spain), Glasgow (United Kingdom), Leeds (United Kingdom), London (United Kingdom), Manchester (United Kingdom)

NCT03829462

PHASE 3

Assessing a Regorafenib-irinotecan Combination Versus Regorafenib Alone in Metastatic Colorectal Cancer Patients

TARGETS
BRAF, KIT, PDGFRs, RAF1, RET, VEGFRs, TOP1

LOCATIONS: Montpellier (France)

NCT03475953

PHASE 1/2

A Phase I/II Study of Regorafenib Plus Avelumab in Digestive Tumors

TARGETS
PD-L1, BRAF, KIT, PDGFRs, RAF1, RET, VEGFRs

LOCATIONS: Bordeaux (France), Montpellier (France), Toulouse (France)

NCT03714958

PHASE 1

Trametinib + HDM201 in CRC Patients With RAS/RAF Mutant and TP53 Wild-type Advanced/Metastatic Colorectal Cancer Mutant and TP53 Wild-type

TARGETS
MDM2, MEK

LOCATIONS: Lyon (France)

NCT02857270

PHASE 1

A Study of LY3214996 Administered Alone or in Combination With Other Agents in Participants With Advanced/Metastatic Cancer

TARGETS
ERK1, ERK2, CDK4, CDK6

LOCATIONS: District of Columbia, Florida, Massachusetts, New Hampshire, Sydney (Australia), Pennsylvania, Sunto-Gun (Japan), Tennessee, Texas, Chuo-Ku (Japan), Nedlands (Australia), Villejuif Cedex (France)

CLINICAL TRIALS

NCT03745989

PHASE 1

Study of MK-8353 + Selumetinib in Advanced/Metastatic Solid Tumors (MK-8353-014)

TARGETS
ERK1, ERK2, MEK

LOCATIONS: Vancouver (Canada), Florida, Toronto (Canada), Texas, Bellinzona (Switzerland)

NCT02934529

PHASE 3

Metastatic Colorectal Cancer (RAS-wildtype) After Response to First-line Treatment With FOLFIR Plus Cetuximab

TARGETS
EGFR, VEGFA, BRAF, KIT, PDGFRs, RAF1, RET, VEGFRs

LOCATIONS: Munich (Germany)

NCT03875820

PHASE 1

Phase I Trial of VS-6063 and RO5126766.

TARGETS
RAFs, MEK, FAK

LOCATIONS: Manchester (United Kingdom), Sutton (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

GENE
PTCH1

ALTERATION
R1308fs*64

RATIONALE
Loss or inactivation of the tumor suppressor PTCH1 upregulates the activity of the Hedgehog pathway member Smoothened (SMO), which may contribute to excessive cell proliferation. Inhibitors of SMO or BET-domain containing transcription factors may be relevant in a tumor with a loss or inactivation of PTCH1. 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.

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Colorado, Massachusetts, Ottawa (Canada), Oregon, Pennsylvania, South Carolina, Melbourne (Australia), Villejuif (France), Barcelona (Spain), Madrid (Spain), Pamplona (Spain)

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Bordeaux (France), Villejuif (France), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Barcelona (Spain), Madrid (Spain)

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD3, BRD4, BRD2, BRDT

LOCATIONS: Massachusetts, Texas, Brussels (Belgium), Bruxelles (Belgium), Gent (Belgium), Leuven (Belgium), Nantes (France), Paris (France), Villejuif (France), Tübingen (Germany)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, Florida, New York, Texas, Virginia

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Kingston (Canada), London (Canada), Ottawa (Canada), Toronto (Canada), Montreal (Canada), Regina (Canada), Saskatoon (Canada)

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4, PARP

LOCATIONS: Toronto (Canada), Florida, Oklahoma, Tennessee

GENE
RNF43

ALTERATION
G659fs*41

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT01351103

PHASE 1

A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands

TARGETS
PORCN, PD-1

LOCATIONS: California, Barcelona (Spain), Maryland, Massachusetts, Michigan, Texas, Rotterdam (Netherlands), Utrecht (Netherlands), Madrid (Spain)

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Sutton (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle (United Kingdom), Oxford (United Kingdom)

GENE
SUFU

ALTERATION
A25fs*23

RATIONALE
Inactivation of SUFU may lead to increased GLI transcriptional activity, which has been shown to be dependent on the BET bromodomain protein BRD4. Therefore, BET inhibitors may be appropriate in the context of a SUFU mutation.

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Colorado, Massachusetts, Ottawa (Canada), Oregon, Pennsylvania, South Carolina, Melbourne (Australia), Villejuif (France), Barcelona (Spain), Madrid (Spain), Pamplona (Spain)

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Bordeaux (France), Villejuif (France), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Barcelona (Spain), Madrid (Spain)

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD3, BRD4, BRD2, BRDT

LOCATIONS: Massachusetts, Texas, Brussels (Belgium), Bruxelles (Belgium), Gent (Belgium), Leuven (Belgium), Nantes (France), Paris (France), Villejuif (France), Tübingen (Germany)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, Florida, New York, Texas, Virginia

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4, PARP

LOCATIONS: Toronto (Canada), Florida, Oklahoma, Tennessee

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.

ABL1
F382fs*3

AKT1
D46E

ALOX12B
L451fs*16

ATM
S1691R

CARD11
R555fs*45

CASP8
L25P

CD22
V508A

CREBBP
Q2214_Q2216del

CTNNA1
R551W

GNAS
R16C

IRS2
A701_V702insA and L1314fs*17

KDM5A
F172fs*5, G1200fs*9 and T1060M

KMT2A (MLL)
E2986K

MERTK
W485C

MRE11A
A440T

MSH3
K383R

NF1
G1129D

NOTCH1
A2069T

NTRK1
S708fs*38

POLD1
T473M

STAG2
V569M

STK11
I99T

WHSC1 (MMSET)
L318S

ZNF703
A524P

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Genomic Signatures and Gene Alterations

Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Genomic signatures and gene alterations detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH.

Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

PDF Service version: 2.6.0

The median exon coverage for this sample is 1,252x

Electronically signed by Richard Huang, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director Foundation Medicine, Inc. | Roche Customer Care: +49 7624 14 2098 or europe.foundationmedicine@roche.com

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Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

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