FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Srivastav, Sanjeev	**12 June 2016**	**Colon adenocarcinoma (CRC)**

Date of Birth	10 July 1974	**Medical Facility**	Max Healthcare	**Specimen Received**	03 June 2016
Sex	Male	**Ordering Physician**	Verma, Amit	**Specimen Site**	Soft Tissue
FMI Case #	TRF158361	**Additional Recipient**	Not Given	**Date of Collection**	31 May 2016
Medical Record #	Not Given	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	15136/15 A2 (16CO2667)	**Pathologist**	Not Provided		

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

27 genomic alterations

5 therapies associated with potential clinical benefit

0 therapies associated with lack of response

26 clinical trials

TUMOR TYPE: COLON ADENOCARCINOMA (CRC)

Genomic Alterations Identified†

BRCA1 K654fs*47
BRCA2 D946fs*14
HRAS G12S
MSH2 G71*
ATM N2586fs*20
CTNNB1 T41I
FBXW7 R479Q
RNF43 G659fs*41, R225fs*194
ARID1B T1639M
ASXL1 G645fs*58
CDC73 G416fs*12
CDH1 L355fs*1
CHD2 V175fs*1
CHD4 K945fs*28
FANCL K300fs*43
FAT1 A4305V
JAK1 K860fs*16
KDM6A W1194*
MLL2 V3089fs*30
NOTCH1 P2512fs*45+
NOTCH2 N1999fs*32
RAD50 K722fs*14
RB1 N123fs*8
RUNX1 R201fs*10
SETD2 S2382fs*29
SMARCA4 Q194fs*109

Additional Disease-relevant Genes with No Reportable Alterations Identified†

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BRAF
KRAS
NRAS

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
BRCA1 K654fs*47	None	Olaparib	Yes, see clinical trials section
BRCA2 D946fs*14	None	Olaparib	Yes, see clinical trials section
HRAS G12S	None	Cobimetinib Trametinib	Yes, see clinical trials section
MSH2 G71*	None	Nivolumab Pembrolizumab	Yes, see clinical trials section
ATM N2586fs*20	None	None	Yes, see clinical trials section
CTNNB1 T41I	None	None	Yes, see clinical trials section
FBXW7 R479Q	None	None	Yes, see clinical trials section
RNF43 G659fs*41, R225fs*194	None	None	Yes, see clinical trials section
ARID1B T1639M	None	None	None
ASXL1 G645fs*58	None	None	None
CDC73 G416fs*12	None	None	None
CDH1 L355fs*1	None	None	None
CHD2 V175fs*1	None	None	None
CHD4 K945fs*28	None	None	None

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Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
FANCL K300fs*43	None	None	None
FAT1 A4305V	None	None	None
JAK1 K860fs*16	None	None	None
KDM6A W1194*	None	None	None
MLL2 V3089fs*30	None	None	None
NOTCH1 P2512fs*45+	None	None	None
NOTCH2 N1999fs*32	None	None	None
RAD50 K722fs*14	None	None	None
RB1 N123fs*8	None	None	None
RUNX1 R201fs*10	None	None	None
SETD2 S2382fs*29	None	None	None
SMARCA4 Q194fs*109	None	None	None

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

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● ***BRCA1*** K654fs*47	**Gene and Alteration:** The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[1]. BRCA1 alterations that disrupt the ring-type zinc finger domain (amino acids 24-65) or BRCT domains (aa 1642-1855), such as observed here, are predicted to result in a loss of function[2,3,4]. Germline mutations in BRCA1 or BRCA2 are associated with breast-ovarian cancer familial susceptibility (BROVCA), also known as hereditary breast-ovarian cancer (HBOC)[5,6]. The lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[7], and elevated risk of other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, at a frequency range of 20-60%[8]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[7,9,10,11,12,13,14]. In the appropriate clinical context, germline testing of BRCA1 is recommended. **Frequency and Prognosis:** In the Colorectal Adenocarcinoma TCGA dataset, somatic mutations in the BRCA1 gene have been reported in 2.7% of tumors[15]. One study reported that 87% of colorectal cancer samples analyzed were positive for BRCA1 protein expression, and that BRCA1 expression was associated with significantly longer overall patient survival[16]. Another study reported that although BRCA1 mutations were not more frequent among unselected patients with colorectal cancer compared to controls, mutations were reported at a higher frequency in patients with either early onset colorectal cancer or familial history of colorectal cancer as compared to controls, suggesting that BRCA1 mutation may increase the risk of early onset or familiar colorectal cancer[17]; however, additional studies are required. Carriers of BRCA1 mutations in an Ashkenazi Jewish population have a 4-fold increase in colon cancer risk[18]. **Potential Treatment Strategies:** Tumors with BRCA1 mutations or reduced BRCA1 protein levels have been reported to be sensitive to DNA-damaging drugs, such as cisplatin and carboplatin, and to PARP inhibitors[19,20,21]. The PARP inhibitor olaparib is FDA approved to treat patients with BRCA1/2-mutant ovarian cancer, and olaparib and other PARP inhibitors are in clinical trials in patients with solid tumors. BRCA1 deficiency has been implicated in resistance to docetaxel or paclitaxel; however, data that are inconsistent with this have also been reported[22].
● ***BRCA2*** D946fs*14	**Gene and Alteration:** The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[23]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[24]. BRCA2 alterations that disrupt PALB2 binding (aa 21-39)[25], the BRC repeats (aa 1002-2085), the DNA binding domain (aa 2479-3192), and/or the C-terminal RAD51 binding domain, such as observed here, are predicted to be inactivating[23,26,27,28,28,29,30,30,31,32,33,34,35,36,37,38]. Germline mutations in BRCA1 or BRCA2 are associated with breast-ovarian cancer familial susceptibility (BROVCA), also known as hereditary breast-ovarian cancer (HBOC)[5,6]. The lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[7], and elevated risk of other cancers, including gastric, pancreatic, prostate, and colorectal tumors, has been identified at frequencies of 20-60%[8,11,39,40,41,42,43,44]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[7,9,10,11,12,13,14]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: BRCA2 mutation has been reported in 4.5% of colorectal adenocarcinoma samples analyzed in the TCGA dataset[15] and in 6.3% of large intestine adenocarcinoma cases in the COSMIC database (COSMIC, Apr 2016). **Potential Treatment Strategies:** BRCA2 alterations may predict sensitivity to DNA-damaging drugs, such as cisplatin or carboplatin, and PARP inhibitors[45]. The PARP inhibitor olaparib is FDA approved to treat patients with BRCA1/2-mutant ovarian cancer, and olaparib and other PARP inhibitors are in clinical trials in patients with solid tumors. In patients with ovarian or breast cancer harboring BRCA1/2 mutation, olaparib has shown promising activity either as monotherapy or in combination with chemotherapy or angiogenesis inhibitors, and achieved clinical benefit in up to 61% of cases[46,47,48,49,50,51,52,53,54,55].
● ***HRAS*** G12S	**Gene and Alteration:** HRAS encodes a member of the RAS family of membrane proteins that bind GDP/GTP and possess GTPase activity. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[56]. HRAS alterations affecting amino acids G12, G13, Q61 and K117, as well as mutations A59T and A146V have been characterized to be activating and oncogenic[56,57,58,59,60,61,62,63,64,65]. **Frequency and Prognosis:** HRAS mutations have been reported in less than 1% of colorectal adenocarcinoma samples in the COSMIC database (May 2016) and have not been reported in the TCGA colorectal adenocarcinoma dataset[15]. A study found somatic HRAS mutations in 4% (2/54) of adenomas and in none of the analyzed (0/6) adenocarcinomas[66]. HRAS protein expression was observed in 65% (61/94) of invasive colorectal adenocarcinomas[67]. **Potential Treatment Strategies:** In preclinical studies, constitutive activation of HRAS has been shown to lead to activation of the RAF-MEK-ERK and PI3K-AKT pathways[68,69]. Therefore, tumors with HRAS amplification or activating mutations may be sensitive to inhibitors of these pathways, which are being evaluated in clinical trials for solid tumors. The MEK inhibitors cobimetinib and trametinib are approved for the treatment of melanoma with BRAF V600E or V600K mutations, and are being studied in clinical trials in solid tumors[70,71]. The reovirus Reolysin targets cells with activated RAS signaling[72,73,74] and is in clinical trials in some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer[75,76,77,78,79,80,81,82,83]. Activating mutations in other RAS family members have been associated with resistance to the anti-EGFR antibodies panitumumab and cetuximab in colorectal cancer (Stintzing et al., 2013; ESMO European Cancer Congress Abstract E17-7073)[84,85,86,87]. Current guidelines from the National Comprehensive Cancer Network (NCCN v3.2014) recommend against the use of cetuximab and panitumumab in patients with known KRAS or NRAS mutations. HRAS activating mutations have been similarly reported to confer resistance to anti-EGFR antibodies in preclinical studies[88].

GENE ALTERATION	INTERPRETATION
● ***MSH2*** G71*	**Gene and Alteration:** MSH2, which encodes the DNA mismatch repair protein MSH2, is a member of the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[89]. MSH2 alterations that may result in loss or disruption of the EXO1 interaction domain (amino acids 601-671), the MutS core domain (aa 303-645), or the nucleotide triphosphate hydrolase domain (aa 619-855), such as observed here, are predicted to be inactivating. Germline mutations of MMR proteins such as MLH1, MSH2, MSH6, or PMS2 are associated with a condition known as Lynch syndrome, which may lead to nonpolyposis colon cancer, gastric cancer, small bowel, or endometrial cancer[90]. In one large study of Lynch syndrome, endometrial cancer was the most common cancer reported outside the colon, with an incidence of 13.8%[91]. For family members of patients with newly diagnosed endometrial cancer, the clinical utility of testing the patient for germline mutations in MMR genes is higher for mutations in MLH1 or MSH2 than it is for MSH6 or PMS2 mutations[92]. Therefore, in the appropriate clinical context, germline testing of MSH2 is recommended. **Frequency and Prognosis:** MSH2 mutations have been reported in 2-10% of colorectal cancer samples analyzed[93,94]. Loss of MSH2 protein has been reported to be rare in colorectal cancer[95,96]. Loss of heterozygosity of chromosome 2p, where MSH2 and MSH6 lie, has been observed in 46% of replication error positive colorectal tumors[97]. MSH2 mutations have been associated with an enhanced risk of developing colorectal cancer[98]. **Potential Treatment Strategies:** MSH2 inactivation leads to MMR defects, MSI, and high mutational burden[99,100,101,102,103], which may predict response to the FDA-approved anti-PD-1 immunotherapies pembrolizumab and nivolumab[104,105,106]. In a Phase 2 study of MSI-high cancers, six patients with MSH2 (germline) mutations reported one partial response and two stable diseases[104]. Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-high CRC compared with microsatellite stable CRC (40% vs. 0%)[104] and its efficacy correlated with high mutational burden in non-small cell lung cancer (NSCLC)[105]. Treatment with nivolumab resulted in a complete response in a patient with MSI-high CRC[106]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[107], potential biomarkers of response to PD-1 targeted immunotherapies. These therapies are in clinical trials for various tumor types and may be appropriate particularly in hypermutant tumors. Preclinical studies have shown that tumor cells deficient in MSH2 are markedly sensitive to methotrexate in vitro[108]. Low levels of MSH2 have been observed by immunohistochemistry (IHC) in NSCLC and may predict benefit to cisplatin-based adjuvant chemotherapy[109,110].
● ***ATM*** N2586fs*20	**Gene and Alteration:** ATM encodes the protein ataxia telangiectasia mutated, a serine/threonine protein kinase that belongs to the PI3K-like protein kinase (PIKK) family and plays a key role in the DNA damage response[111]. ATM is recruited to sites of DNA double-strand breaks and acts as a signal transducer that coordinates DNA repair, cell cycle checkpoints, and apoptosis in response to DNA damage[111]. Loss of functional ATM promotes tumorigenesis[112] and mutations in ATM underlie the rare autosomal recessive inherited disorder ataxia-telangiectasia that is characterized by genomic instability, sensitivity to DNA-damaging agents and increased risk of developing cancer[111]. ATM mutations that disrupt or remove the protein kinase domain (amino acids 2712-2962) or the FATC domain (amino acids 3024–3056), such as observed here, are predicted to result in loss of function[113]. **Frequency and Prognosis:** ATM mutations have been reported in 11% of cases in the Colorectal Adenocarcinoma TCGA dataset[15]. Loss of heterozygosity (LOH) of ATM has been observed in 23-31% of distal colon cancers, but not in proximal colon tumors[114]. Expression of ATM in patients with colorectal cancer (CRC) has been associated with longer survival[16].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair, and may predict sensitivity to PARP inhibitors[115] such as olaparib. Several preclinical studies have shown that loss of functional ATM confers moderate sensitivity to PARP inhibitors[116,117,118,119,120], with some studies reporting increased sensitivity specifically in cells with loss of both ATM and TP53[121,122]; one preclinical study reported that ATM depletion did not increase sensitivity to PARP inhibitors[123]. In a Phase 2 trial, 4/5 patients with ATM-mutated castration-resistant prostate cancer benefited from olaparib treatment[124]. In a Phase 2 study of patients with gastric cancer, the combination of olaparib with paclitaxel resulted in improved overall survival versus paclitaxel alone, both in the overall patient population and the patient population with low ATM protein expression[125]. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells, and were active in a lymphoma mouse model lacking ATM activity, suggesting a potential therapeutic strategy for tumors with inactivating ATM mutations[126].
● ***CTNNB1*** T41I	**Gene and Alteration:** CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[127]. CTNNB1 exon 3 mutations, such as observed here, are considered to be activating in that they lead to increased beta-catenin protein stability and activation of the WNT pathway[128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145]. **Frequency and Prognosis:** CTNNB1 mutations have been reported in 5-7% of colorectal adenocarcinomas[15,146,147]. Overexpression of beta-catenin has been observed in up to 80% of colorectal tumors, resulting in activation of the WNT/beta-catenin pathway[148,149,150]. Findings concerning the association between beta-catenin expression and prognosis in patients with colorectal cancer have been conflicting, with some studies correlating expression with better overall survival and other studies associating beta-catenin expression with poor overall survival[148,151,152,153]. **Potential Treatment Strategies:** Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[154,155,156]. The mTOR inhibitors everolimus and temsirolimus are FDA approved in various indications and have shown clinical activity in patients with endometrial carcinoma and CTNNB1 mutations (Myers et al., 2015; ASCO Annual Meeting Abstract 5592)[157]. A patient with recurrent hepatocellular carcinoma and a CTNNB1 mutation, who had progressed on sorafenib monotherapy, experienced tumor regression and clinical benefit upon combination treatment with everolimus and sorafenib[158]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[159,160,161,162]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases (Kummar et al., 2015; ASCO Abstract 10563)[163]. Therefore, CTNNB1-mutant tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutant cells, clinical data supporting this therapeutic approach is lacking[155,164,165,166].

GENE ALTERATION	INTERPRETATION
● ***FBXW7*** R479Q	**Gene and Alteration:** FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[167]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[167,168]. Alterations that disrupt the dimerization domain (aa67-90)[169,170], F-box domain (aa278-324)[171], or WD40 repeats (aa378-659)[172], including hot spot residues R465, R479, or R505, are likely to result in failure to target its substrates for degradation and to promote tumorigenesis[168,173,174,175]. **Frequency and Prognosis:** Mutations in FBXW7 have been identified in 9-21% of colorectal adenocarcinomas[15,146,147]. FBXW7 has been reported to be the fourth most commonly mutated gene in colorectal cancer, with mutations in 6-10% of cases in the scientific literature[176,177,178]. Mutations in FBXW7 have also been identified in 4-7% of colorectal adenomas[177,179]. Low FBXW7 mRNA levels are associated with poor patient prognosis, and FBXW7 inactivation in colorectal cancer has been associated with chromosomal instability[177,180]. **Potential Treatment Strategies:** Preclinical studies indicate that loss or inactivation of FBXW7 may predict sensitivity to mTOR inhibitors, such as the FDA-approved therapies everolimus and temsirolimus[181,182]. In two case reports, temsirolimus elicited a radiographic response in a patient with FBXW7-mutant lung cancer[183], and a patient with FBXW7-mutated papillary renal cell carcinoma responded to everolimus for 13 months[184]. In another study, 7/10 patients with FBXW7 mutations in different tumor types achieved stable disease for 2.2-6.8+ months upon treatment with various mTOR inhibitors[185]. However, several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer, including those whose tumors harbor alterations in PIK3CA and/or PTEN, and that resistance may occur at least in part through activation of the RAS-MAPK pathway[186,187,188]. Combination therapies may be required to overcome this resistance, as demonstrated by both preclinical and clinical studies evaluating the efficacy of mTOR inhibitors in combination with sorafenib[189], other inhibitors of the VEGF signaling pathway[190,191], or inhibitors of BCL2 family proteins[192]. Reduction in FBXW7 was reported to result in accumulation of the FBXW7 substrates NOTCH1, c-MYC, and cyclin E[193], but therapeutic strategies targeting these proteins have not been tested in the context of FBXW7 inactivation (Dombret et al., 2014; ASH Abstract 117, Thieblemont et al., 2014; ASH Abstract 4417)[194,195,196,197,198,199,200]. FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[201].
● ***RNF43*** G659fs*41, R225fs*194	**Gene and Alteration:** RNF43 encodes a ubiquitin ligase[202] that was discovered because it is overexpressed in colon cancer[203]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[204,205,206,207,208]. An additional tumor suppressor-like role for RNF43 in colon cancer is hypothesized to be its interaction with the ubiquitin protein ligase NEDL1, which is believed to enhance the pro-apoptotic role of p53[209]. **Frequency and Prognosis:** RNF43 mutations have been reported to occur in 18-27% of endometrial cancers[210,211], 3-5% of pancreatic cancers[212], 21% of ovarian mucinous carcinomas[213], 9% of liver fluke-associated cholangiocarcinomas[214], and up to 18% of colorectal cancers[15,211]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[211], endometrial[211], and gastric cancers[215,216]; one study reported RNF43 alterations in >50% of MSI gastric carcinomas[215].

GENE ALTERATION	INTERPRETATION
	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[204,205,206,207,208]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.
ARID1B T1639M	**Gene and Alteration:** ARID1B encodes the AT-rich interactive domain-containing protein 1B, also known as BAF250B, which is a member of the SWI/SNF chromatin remodeling complex. Germline mutations in ARID1B and in other SWI/SNF component genes have been identified in the developmental disorder Coffin-Siris syndrome[217]. ARID1B and many other members of this complex have been identified as tumor suppressors in a wide range of tumors[218]. **Frequency and Prognosis:** In TCGA datasets, ARID1B alterations have been reported with highest incidence in stomach adenocarcinoma (12%), skin cutaneous melanoma (11%), bladder urothelial carcinoma (9%), lung adenocarcinoma (8%), liver hepatocellular carcinoma (6%), colorectal adenocarcinoma (6%), and lung squamous cell carcinoma (6%) (cBioPortal, 2016). ARID1B deletions have been reported in the B-cell lymphoma Waldenstrom macroglobulinemia[219]. In one study, exome sequencing of MSI CRC patients revealed that ARID1B was frequently mutated (13%, 4/46)[220]. Low level ARID1B expression levels were associated with tumor progression in gastric carcinoma[221]. In neuroblastoma ARID1B mutations were observed in 11% (8/71) of tumors and alterations in ARID1 genes were associated with more aggressive disease and reduced survival[222]. **Potential Treatment Strategies:** There are no targeted therapies to address the inactivation of ARID1B. In a preclinical study, mutant ARID1B failed to repress Wnt/beta-catenin pathway due to decreased BRG1 and beta-catenin interaction, which may indicate Wnt pathway is activated in tumors with ARID1B loss of function[223].
ASXL1 G645fs*58	**Gene and Alteration:** ASXL1 (additional sex combs-like 1) encodes a chromatin-binding protein involved in transcriptional regulation through interaction with the polycomb complex proteins and various other transcriptional regulators[224,225]. Germline inactivating mutations affecting ASXL1 underlie the very rare developmental disorder Bohring-Opitz syndrome[226]. ASXL1 alterations that remove the PHD domain (amino acids 1491-1541), including truncating mutations and deletions, lead to aberrant epigenetic regulation[225,227,228]. **Frequency and Prognosis:** ASXL1 mutations have been reported in various solid tumors, including 4% of colorectal cancers[147], 3% of breast cancers[229], 2% of hepatocellular carcinomas[230], 2% (1/61) of prostate cancers[231], and 1.4% (1/74) of head and neck squamous cell carcinomas[232]. ASXL1 amplification has also been reported in 5.1% of cervical cancers[233]. ASXL1 mutations have mainly been studied and reported in the context of hematological malignancies, where they have been correlated with poor prognosis in myelodysplastic syndromes, chronic myelomonocytic leukemia, acute myeloid leukemia, and myeloproliferative neoplasms[224,227,234]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in ASXL1.

GENE ALTERATION	INTERPRETATION
● ***CDC73*** G416fs*12	**Gene and Alteration:** CDC73 encodes parafibromin, a component of the PAF protein complex[235]. PAF complexes with BCL9, PYGO, and beta-catenin to assemble a nuclear Wnt-signaling complex[236]. Parafibromin has been reported to inhibit MYC, CCND1[237,238,239,240,241], as well as cell proliferation[241,242,243,244]. It can also activate or inhibit beta-catenin signaling, depending on context[236,245,246]. Inactivating germline mutations in CDC73 are causal in hyperparathyroidism-jaw tumor syndrome[247], and frequent somatic mutation has been documented in parathyroid carcinoma (PC); however, CDC73 mutation is rare in benign parathyroid adenoma[248]. Heterozygous germline inactivation of CDC73 has additionally been suggested to be a predisposing factor for PC[249]. **Frequency and Prognosis:** Loss of parafibromin expression and to some extent CDC73 mutation has been correlated with higher incidence of metastasis, disease recurrence, and in some cases decreased overall survival in PC patients[250,251]. CDC73 down-regulation has also been observed in oral squamous cell carcinomas (OSCC), and knockdown of CDC73 results in increased cell viability and proliferation in preclinical OSCC models[242,243]. **Potential Treatment Strategies:** At present there are no targeted therapies available to address genomic alterations in CDC73.
● ***CDH1*** L355fs*1	**Gene and Alteration:** CDH1 encodes the transmembrane protein E-cadherin, which plays an important role in epithelial cell-cell adhesion and tissue morphogenesis[252]. Loss of E-cadherin expression leads to decreased cellular adhesion and results in cell migration and cancer metastasis[253,254,255,256]. CDH1 alterations that remove or disrupt critical domains of E-cadherin, including extracellular cadherin domains (amino acids 155-709), juxtamembrane domain (amino acids 734-783), and catenin binding domain (amino acids 811-882) are predicted to be inactivating[257,258,259,260,261]. Germline mutations in CDH1 are highly associated with hereditary diffuse gastric cancer (HDGC) and present in 25-50% of HDGC cases[262,263,264]. Germline CDH1 mutations have also been implicated in invasive lobular breast carcinoma[265,266,267,268]. **Frequency and Prognosis:** CDH1 mutations have been reported in 1-3% of colorectal adenocarcinomas[146,147]. E-cadherin functions as an 'invasion-suppressor' protein in colorectal carcinomas; loss of function or expression contributes to cellular proliferation, invasion and metastasis[269,270]. In a majority of tumors, downregulation of E-cadherin is caused by transcriptional repression and epigenetic silencing by methylation, not by gene mutations[271,272,273]. Germline CDH1 mutations have been reported to be associated with early-onset colorectal cancer[274]. Loss of E-cadherin expression, and subsequent colon tumor budding, is associated with poor prognosis and short survival[275,276,277,278]. **Potential Treatment Strategies:** There are no available drugs to compensate directly for CDH1 mutation or loss, or E-cadherin inactivation.
● ***CHD2*** V175fs*1	**Gene and Alteration:** CHD2 encodes chromodomain helicase DNA binding protein 2, an ATPase/helicase that alters gene expression by modifying chromatin structure. Germline deletions and mutations in CHD2 are associated with several epilepsy syndromes, including Dravet syndrome and Lennox-Gastaut syndrome[279,280,281].

GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: Somatic mutations in CHD2 have been reported in 1% of all cancers in COSMIC, and including in 7% of pituitary, 6% of colorectal, 4% of skin, and 3% of urinary tract cancers (COSMIC, 2016). Loss-of-function mutations in CHD2 have been observed in nearly 50% of MSI-high colorectal and gastric cancers[282], and differential expression of CHD2 was reported to be associated with colon cancer progression[283]. Deletion of this gene has also been observed in a Hodgkin lymphoma cell line[284]. In agreement with these findings, preclinical research has suggested that CHD2 is a tumor suppressor that plays roles in the DNA damage response[285]. **Potential Treatment Strategies:** There are no therapies available to directly address genomic alterations in CHD2.
● ***CHD4*** K945fs*28	**Gene and Alteration:** CHD4 encodes chromodomain helicase DNA binding protein 4 (also called Mi2-beta or Mi2b), a core catalytic subunit of the nucleosome remodeling and deacetylase (NuRD) complex. The NuRD complex is an epigenetic regulator that can activate or repress the transcription of target genes, and it has been shown to play a role in stem cell function and oncogenesis[286,287]. **Frequency and Prognosis:** CHD4 mutations are found in up to 18% in gynecological cancers and are especially prevalent in endometrial and uterine cancers, while CHD4 amplification is reported most commonly in testicular germ cell tumors (20%), ovarian cancer (10%), and low-grade glioma (7%) (COSMIC, cBioPortal, 2016). One study reported CHD4 mutations in 8% (5/63) of microsatellite-unstable gastric and colorectal cancers but in none of the 90 evaluated microsatellite-stable gastric and colorectal cancers[282]. Several preclinical studies have suggested that CHD4 may be an oncogene. One study reported that CHD4 and the NuRD complex cooperate with DNA methyltransferases to silence tumor suppressor genes in colorectal cancer[288], whereas a second study found that CHD4 drives a large-scale gene expression program in glioblastoma tumor-initiating cells and plays essential roles in the maintenance of the stem-cell-like, tumorigenic state of these cells[289]. However, other studies have reported that CHD4 can have NuRD-independent functions in the DNA damage response and thereby acts as a tumor suppressor[290]. In one preclinical study, CHD4 depletion sensitized cells to DNA damaging agents such as etoposide and camptothecin, as well as to PARP inhibitors[291]. **Potential Treatment Strategies:** There are no therapies available to directly address genomic alterations in CHD4.
● ***FANCL*** K300fs*43	**Gene and Alteration:** FANCL encodes a member of the Fanconi anemia nuclear complex, a multiprotein structure also including the products of FANCA, FANCC, FANCF and FANCG. The activity of this complex is essential to prevention of chromosome breakage caused by DNA damage[292]. Germline mutations in FANCL cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair[293]. **Frequency and Prognosis:** Somatic mutations in FANCL are infrequently observed (<1%) in human malignancies (COSMIC, 2016). **Potential Treatment Strategies:** There are no targeted therapies that directly address genomic alterations in FANCL.

GENE ALTERATION	INTERPRETATION
● ***FAT1*** A4305V	**Gene and Alteration:** FAT1 encodes a protocadherin protein which normally promotes actin polymerization and cell migration, and has been shown to block beta-catenin nuclear localization and inhibit transcriptional activity. FAT1 inactivation leads to upregulated WNT signaling and may contribute to tumorigenesis[294]. **Frequency and Prognosis:** FAT1 loss is frequent in cancer; FAT1 deletion has been observed in 80% of primary oral cancers and correlates with a transition from ductal to invasive breast cancer[295]. FAT1 mutations have been reported in glioblastoma (20.5%), colorectal cancer (7.7%), and head and neck cancer (6.7%)[294]. FAT1 may function differently in hematopoietic malignancies, as FAT1 expression is upregulated in multiple types of leukemia and has been associated with poor patient prognosis[295]. **Potential Treatment Strategies:** There are no therapies available to directly address FAT1 genomic alterations.
● ***JAK1*** K860fs*16	**Gene and Alteration:** The JAK1 (Janus kinase 1) gene encodes a tyrosine kinase that regulates signals triggered by cytokines and growth factors[296]. Dysregulation of JAK/STAT signaling has been implicated in a variety of epithelial tumors[297]. However, JAK/STAT signaling is required for the antiviral and antiproliferative effects of interferons[298]. JAK1 alterations that result in the disruption or loss of the kinase domain (875-1153), such as seen here, are predicted to be inactivating. JAK1 truncating mutations have been reported in approximately 8% of gynecological tumors in one study and characterized to be defective for interferon-gamma-induced tumor antigen presentation, suggesting that JAK1 truncating mutations could contribute to tumor immune evasion in gynecologic cancers[299]. **Frequency and Prognosis:** JAK1 mutations have been reported in 2-4% of colon adenocarcinoma samples analyzed (COSMIC, cBioPortal, Dec 2015). JAK1 mutation in colorectal cancer has not been extensively studied in the scientific literature (PubMed, Dec 2015). JAK/STAT pathway components JAK1, JAK2, and STAT3 have been found to be involved in cell growth, survival, invasion, and migration in colorectal cancer cells, and nuclear localization of phospho-STAT3 was noted in colorectal adenomas and adenocarcinomas as compared to normal colonic epithelium[300]. JAK1-mediated activation has been reported to promote chemotherapy and MEK inhibitor resistance in colorectal cells[301,302]. Most transforming JAK1 mutations show increased tyrosine phosphorylation and activation of downstream signaling pathways, although the degree of transforming ability does not correspond closely to these factors[303]. **Potential Treatment Strategies:** Inhibitors of the JAK/STAT pathway are under development. The JAK1/JAK2 inhibitor ruxolitinib is FDA approved to treat myelofibrosis, and has shown efficacy in reducing symptoms in Phase 1 and 2 trials in patients with myeloproliferative disorders[304,305,306]. Other small molecule inhibitors of JAK1 are being investigated in preclinical studies in some types of solid tumors[307,308]. Hsp90 inhibitors are also being investigated in preclinical studies to target components of the JAK/STAT pathway such as JAK1[309]. However, as the mutation reported here is predicted to be inactivating, these therapeutic approaches would not be relevant.
● ***KDM6A*** W1194*	**Gene and Alteration:** KDM6A encodes UTX, a histone H3 lysine 27 demethylase that functions as a transcriptional regulator[310]. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor[310].

GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: In the COSMIC database, KDM6A mutations have been reported in 2% of samples analyzed, with the highest incidence in tumors of the urinary tract (16%) and salivary gland (7%, 6/87) (COSMIC, 2016). KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)[311], adenoid cystic carcinoma (6.7%)[312], and metastatic prostate cancer (10%)[231]. KDM6A inactivation has been found as a recurrent tumorigenic event in male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to therapies targeting histone H3 lysine 27 methylation in preclinical assays[313]. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer[314,315,316]. **Potential Treatment Strategies:** There are no therapies available to address KDM6A alterations.
● ***MLL2*** V3089fs*30	**Gene and Alteration:** MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[317]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[318]. **Frequency and 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[319]. MLL2 alterations are also observed in a number of solid tumor contexts (COSMIC, 2016), being especially prevalent in squamous cell lung carcinoma[320]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in MLL2.
● ***NOTCH1*** P2512fs*45+	**Gene and Alteration:** NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene[321,322]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis[323,324]. NOTCH1 truncation mutations that disrupt the PEST domain (amino acids 2424-2555), such as observed here, have been shown to stabilize intracellular NOTCH1 and cause a modest increase in activity[325,326]. **Frequency and Prognosis:** NOTCH1 mutations have been reported in 5% of colorectal carcinoma cases (COSMIC, May 2016). NOTCH1 protein expression levels correlate with colorectal disease progression, being found in 7.7% of patients with ulcerative colitis, 14.7% of patients with colorectal adenoma, and 58% of patients with colorectal cancer[327]. NOTCH1 protein has been found to be enriched in colorectal cancers compared to normal tissues, and high levels of NOTCH1 are associated with poor prognosis[327,328,329]. **Potential Treatment Strategies:** NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be a potential therapeutic approach in the case of NOTCH1 activating mutations[194,195,330,331,332,333,334,335]. A complete response to the GSI BMS-906024 was achieved in a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation (Knoechel et al., 2015; doi: 10.1101/mcs.a000539); BMS-906024 has been shown to have pan-NOTCH signaling inhibitory activity in vitro and anti-tumor efficacy in xenograft models of leukemia and triple-negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression[336].

GENE ALTERATION	INTERPRETATION
● ***NOTCH2*** N1999fs*32	**Gene and Alteration:** NOTCH2 encodes a member of the NOTCH family of receptors, which play a role in cell fate determination and various developmental processes. Upon binding of membrane bound ligands, NOTCH signaling involves gamma-secretase (GS) cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[323,324]. Depending on cellular context, NOTCH2 can act as either a tumor suppressor or an oncogene[321,337,338,339,340]. NOTCH2 alterations that disrupt or remove the ANK repeat region (amino acids 1876-2041), such as seen here, are predicted to be inactivating[341,342]. **Frequency and Prognosis:** In the TCGA dataset, NOTCH2 mutation was observed in 5% of colorectal adenocarcinoma cases and NOTCH2 homozygous deletion was observed in fewer than 1% of cases[15]. In a study of over 1000 patients with colorectal cancer, loss of NOTCH2 protein expression predicted adverse prognosis and was significantly associated with poor overall survival[329]. **Potential Treatment Strategies:** Several approaches for inhibiting NOTCH2 signaling have been developed, including neutralizing Notch antibodies such as OMP-59R5[343], which targets NOTCH2 and NOTCH3, and pan-Notch inhibitors, such as gamma-secretase inhibitors (GSI). A Phase 1b study of OMP-59R5 in combination with gemcitabine and nab-paclitaxel has shown promising efficacy (up to 50% partial response) in patients with untreated metastatic pancreatic cancer (O'Reilly et al., 2015; Gastrointestinal Cancers Symposium Abstract 278). A Phase 1b study of OMP-59R5 in combination with etoposide and cisplatin for small cell lung cancer reported a median progression free survival of 124 days and 84% overall response rate (Pietanza et al., 2015; ASCO Abstract 7508). The GSI BMS-906024 inhibits NOTCH activity in vitro and exhibits anti-tumor activity in xenograft models of leukemia and triple negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression[336]. These agents are being investigated in preclinical studies and early clinical trials in various tumor types[344]. While activating mutations may be targeted via gamma-secretase inhibitors, there are no therapies available to address NOTCH2 inactivation, as seen here.
● ***RAD50*** K722fs*14	**Gene and Alteration:** RAD50 binds to MRE11 and NBS1 to form the MRE-RAD50-NBS1 (MRN) complex. The MRN complex regulates DNA double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiotic recombination[345]. RAD50 contains three critical regions that are primarily responsible for its function: the central coiled-coil domain (amino acids 228-1079), the zinc-hook loop (amino acids 635-734), and an ATPase domain formed by portions from both the N and C termini (amino acids 1-45 and 1201-1238). Mutations truncating the RAD50 coiled-coil domain have been shown to negatively impact homologous recombination and nonhomologous end-joining and to inhibit telomere maintenance and meiotic double-strand break (DSB) formation[346]. **Frequency and Prognosis:** RAD50 is mutated at a relatively high frequency in colorectal and endometrial cancers (2-9%) and at lower frequencies across a range of solid tumors (cBioPortal, COSMIC, 2016). Germline mutations in RAD50 have been reported in hereditary breast and/or ovarian cancer (HBOC), but they are rare and not significantly associated with increased risk of cancer[347,348]. High expression of MRE11 or NBS1 protein or the entire MRN complex was shown to be associated with microsatellite stability, earlier tumor stage, and longer survival in patients with colorectal cancer (CRC)[349].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: There are no targeted therapies approved or in clinical trials that directly address genomic alterations in RAD50. Deficiencies in or disruption of MRN complex components have been shown to sensitize cancer cells to PARP inhibitors, including those under investigation in clinical trials[350,351,352,353,354]. However, conflicting results have been reported regarding whether depletion of RAD50 specifically confers sensitivity to PARP inhibitors[351,353]. In a preclinical study, CRC cells with mutations in both MRE11 and RAD50 were highly sensitive to irinotecan[355], and other studies have reported that disruption of RAD50 sensitizes human cancer cells to cisplatin[356,357]. Furthermore, a case report described a patient with metastatic small cell carcinoma who was treated with a combination of irinotecan and a CHK1/2 inhibitor and achieved a durable complete response that has continued more than 3 years after discontinuation of drug therapy; the study showed that the patient's tumor harbored a destabilizing RAD50 mutation and that RAD50 loss or inactivation moderately sensitizes cells to topoisomerase I inhibitors and provides far stronger sensitivity to such agents in the setting of ATR or CHK1 inactivation[358].
RB1 N123fs*8	**Gene and Alteration:** RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[359,360]. RB1 alterations that disrupt or remove the pocket domain (aa 373-771) and/or the C-terminal domain (aa 773-928), such as observed here, are predicted to be inactivating[361,362,363,364,365,366,367]. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[368]. Germline mutations in RB1 account for approximately 40% of RB tumors[369] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[370,371]. In the appropriate clinical context, germline testing of RB1 is recommended. **Frequency and Prognosis:** In TCGA dataset, mutation of RB1 has been found in 2.2% of colorectal adenocarcinoma cases[15]. Although RB1 loss is frequent in many types of cancer, RB1 amplification and/or overexpression has been reported in colorectal cancer, with RB1 mRNA overexpression detected in 37.5% of colorectal tumors and Rb expression found in 83-88% of cases[372,373,374,375]. **Potential Treatment Strategies:** There are no therapeutic options to target the activation or inactivation of Rb. Preclinical studies are actively investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, BCL2 family inhibitors, and NOTCH pathway activation[376,377,378]. Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer[360,379]. RB1 inactivation predicts resistance to CDK4/6 inhibitors that act upstream of Rb[380,381,382,383].
RUNX1 R201fs*10	**Gene and Alteration:** RUNX1 encodes a transcription factor that is involved in developmental gene expression programs and hematopoiesis. It is a frequent site of translocation and mutation in myeloid cancers, and it functions as a tumor suppressor in this context[384,385]. Reports of RUNX1 translocations and mutations in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are common. RUNX1 plays a context-dependent role in epithelial cells and has been implicated as both a tumor suppressor and oncogene in different types of solid tumors[386]. RUNX1 alterations that result in loss or disruption of the RUNT domain (amino acids 50–178) or C-terminal transactivation domain (amino acids 291–371), including alterations at residues R107 (also known as R80), K110 (K83), L144 (L117), D198 (D171), R201 (R174), or R204 (R177) and the mutation R172G (R135G)[387,388,389,390,391,392], as observed here, are predicted to be inactivating.

GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: RUNX1 mutations have been reported in 0-5% of colorectal adenocarcinomas (cBioPortal, COSMIC, Nov 2015)[15,146]. Some RUNX1 alterations have been reported to be significantly associated with increased risk of colon cancer, and to be associated with increased risk of rectal cancer, though the rectal association was not statistically significant[393]. A preclinical study showed that RUNX1 deficiency in intestinal epithelial cells enhanced tumor formation in APC- mice and promoted tumor formation in APC+ mice, indicating that RUNX1 acts as a tumor suppressor in colon cancer[394]. **Potential Treatment Strategies:** There are no therapies available to directly target inactivating alterations in RUNX1. Limited clinical (Kuendgen et al., 2013; ASH Abstract 2757)[395] and preclinical[396] data suggest that RUNX1 alterations, rearrangements in particular, may be associated with sensitivity to DNMT inhibitors, such as the approved agents azacitidine and decitabine. However, multiple clinical studies have reported that RUNX1 is not a significant biomarker for efficacy of these therapies (Kuendgen et al., 2013; ASH Abstract 2757, Guadagnuolo et al., 2014; ASH Abstract 1030)[397,398]. Similarly, on the basis of limited clinical[399] and preclinical[400,401,402] evidence, RUNX1 rearrangements may predict sensitivity to HDAC inhibitors. However, further studies are required to establish clinical significance.
● ***SETD2*** S2382fs*29	**Gene and Alteration:** SETD2 encodes a histone lysine-36 methyltransferase[403] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[404]. 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[405]. **Frequency and Prognosis:** Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[406]. SETD2 mutations have been detected in 6-12% of acute lymphoblastic leukemias (ALL) and reportedly increase chromosomal abnormalities and contribute to leukemia development[407,408,409]. **Potential Treatment Strategies:** There are no targeted therapies available to address genomic alterations in SETD2.
● ***SMARCA4*** Q194fs*109	**Gene and Alteration:** SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[410]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[218]. Alterations in SMARCA4 that disrupt or remove the ARID1A-interaction domain (aa 476-587)[411], ATP-binding domain (aa 766-931), or the bromodomain (aa 1477-1547)[412] are predicted to result in loss of SMARCA4 function. Certain point mutations, including T910M and G1232D, have also been characterized to inactivate SMARCA4[413]. **Frequency and Prognosis:** Mutation of SMARCA4 has been documented in 3-6% of colorectal carcinoma (CRC) cases (COSMIC, Feb 2016)[15]. Expression of BRG1 has been reported to be elevated in CRC, and knockdown of BRG1 decreased cell proliferation and cyclin D1 expression in CRC cell lines[414]. Loss of BRG1 expression has been shown to correlate with a poor patient prognosis in some cancers, while in others, elevated BRG1 expression is associated with poor patient prognosis[415,416].

GENE ALTERATION	INTERPRETATION

Potential Treatment Strategies: There are no therapies that directly address mutant SMARCA4 or loss of functional BRG1. However, on the basis of both clinical (Italiano et al., 2015; ECC Abstract 302, Penebre et al., 2015; EORTC Abstract C87) and preclinical (Penebre et al., 2015; EORTC Abstract C87)[417] data, patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with inhibitors of EZH2. In preclinical studies, cells with dual inactivation of SMARCA4 and SMARCA2, which is characteristic of SCCOHT[418,419], were sensitive to EZH2 inhibitors (Penebre et al., 2015; EORTC Abstract C87)[417], and two patients with SCCOHT experienced clinical benefit (1 partial response, 1 long-term stable disease) upon treatment with the EZH2 inhibitor tazemetostat (Italiano et al., 2015; ECC Abstract 302, Penebre et al., 2015; EORTC Abstract C87). Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[420]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[421].

THERAPIES

There are no approved therapies in this patient's tumor type that are specific to the reported genomic alterations.

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Olaparib	**Approved Indications:** The PARP inhibitor olaparib is FDA approved for the treatment of advanced ovarian cancer with deleterious or suspected deleterious germline BRCA mutations. **Gene Association:** Based on extensive clinical evidence in ovarian cancer[46,47,48,49,50] as well as strong clinical evidence in multiple other cancer types[46,49,51,52,124,422], loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib. **Supporting Data:** A Phase 2 study reported olaparib monotherapy to be ineffective for patients with genomically unselected colorectal cancer and disease progression on prior standard systemic therapy, regardless of microsatellite status[423]. Olaparib has been studied primarily for the treatment of ovarian cancer and has resulted in significantly higher response rates for patients with BRCA1/2 mutations than for those without[46,49]. Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, or pancreatic cancer and BRCA1/2 mutations[46,49,51,52,422].
Cobimetinib	**Approved Indications:** Cobimetinib is a MEK inhibitor that is FDA approved in combination with vemurafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. **Gene Association:** HRAS amplification or activating mutations may result in activation of the MAPK pathway and may predict sensitivity to MEK inhibitors, such as cobimetinib. **Supporting Data:** Cobimetinib has been investigated primarily in the context of BRAF V600-mutant melanoma. A Phase 3 study with 495 patients treated either with the BRAF inhibitor vemurafenib plus cobimetinib or vemurafenib alone reported a 68-70% overall response rate, 9.9-12.3 months progression-free survival, and a lower rate of cutaneous squamous cell carcinoma in the combination group; disease progression did not correlate with concurrent alterations in the RAS pathway (Larkin et al., 2015; ASCO Abstract 9006)[70]. In a Phase 1b study, vemurafenib combined with cobimetinib achieved an objective response rate of 87% for patients with BRAF V600-mutant melanoma who had not previously received a BRAF inhibitor[424]. One study reported near-complete response to vemurafenib in a patient with BRAF V600K-mutant melanoma who subsequently developed chronic myelomonocytic leukemia (CMML) with NRAS G12R mutation, and concurrent cobimetinib treatment led to suppression of CMML[425]. In a Phase 1b study, out of 47 patients treated with cobimetinib and the AKT inhibitor ipatasertib, 3 patients with KRAS-mutant ovarian, mesonephric cervical, or endometrial carcinoma had a partial response, with prolonged stable disease lasting for >6 months (Bendell et al., 2014; AACR Abstract CT328).
Trametinib	**Approved Indications:** Trametinib is a MEK inhibitor that is FDA approved as both a single agent and in combination with dabrafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. **Gene Association:** Constitutive activation of HRAS leads to the activation of the MAPK pathway[56]. Therefore, activating mutations in HRAS may predict sensitivity to MEK inhibitors such as trametinib.

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[426,427]. In addition, preclinical investigations have shown sensitivity to trametinib in cell lines with activating KRAS mutations in codons 12, 13, and 61[428]. Phase 1 and Phase 1b studies of trametinib, alone or in combination with gemcitabine, reported some activity in several types of solid tumors[429,430]. 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[431,432]. 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 (Hochster et al., 2013; ASCO GI Abstract 380). 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 (Juric et al., 2014; ASCO Abstract 9051). 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 (Sullivan et al., 2015; AACR-NCI-EORTC Abstract PR06). However, a Phase 1b trial of a combination of trametinib and the mTOR inhibitor everolimus in patients with solid tumors reported frequent adverse events and the study was unable to identify a recommended Phase 2 dose and schedule for the combination[433]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[430,432,434,435], the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear (Tsimberidou et al., 2013; ASCO Abstract e22086).

Nivolumab

Approved Indications: Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is FDA approved to treat unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved to treat non-small cell lung cancer (NSCLC) following disease progression on prior treatments, advanced renal cell carcinoma following antiangiogenic therapy, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

Gene Association: Inactivation of MSH2 has been associated with increased MSI and mutational burden[99,100,101,102,103], and may confer sensitivity to anti-programmed death 1 (PD-1) immune checkpoint inhibitors such as nivolumab[106].

	Supporting Data: Nivolumab has been studied primarily for the treatment of melanoma, NSCLC, and renal cell carcinoma[436,437,438,439,440,441,442,443,444]. In a Phase 3 trial for treatment-naïve patients with metastatic melanoma, the combination of nivolumab and ipilimumab resulted in progression-free survival of 11.5 months, versus 6.9 months with nivolumab or 2.9 months with ipilimumab monotherapies[438]. Nivolumab, as compared with docetaxel, significantly increased overall survival (OS) in patients with platinum-refractory squamous NSCLC (9.2 vs. 6.0 months)[441] and with non-squamous NSCLC (12.2 vs. 9.4 months)[442]. A Phase 3 study compared nivolumab with everolimus for patients with renal cell carcinoma who had received previous antiangiogenic therapy and showed longer median OS (25.0 months vs. 19.6 months) and higher objective response rate (ORR) (25% vs. 5%) with nivolumab than with everolimus[444]. A Phase 2 study of nivolumab for patients with platinum-resistant ovarian cancer reported an ORR of 15% (3/20), a disease control rate of 45% (9/20), and median OS of 20 months at study termination[445]. In patients with small cell lung cancer and progression on platinum-based chemotherapy, nivolumab alone or combined with the immunotherapy ipilimumab achieved ORRs of 18% (7/39) and 17% (7/42), respectively (Calvo et al., 2015; ECC Abstract 3098). Nivolumab demonstrated an ORR of 87% (4/23 complete response, 16/23 partial response, 3/23 stable disease) in patients with Hodgkin lymphoma, which frequently harbors copy gains in the genes encoding PD-L1 and PD-L2 (Ansell et al.,2015; ASH Abstract 583)[446].
Pembrolizumab	**Approved Indications:** Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat unresectable or metastatic melanoma and PD-L1-positive metastatic non-small cell lung cancer (NSCLC) refractory to prior therapy. **Gene Association:** Inactivation of MSH2 has been associated with increased MSI and mutational burden and may confer sensitivity to anti-programmed death 1 (PD-1) immune checkpoint inhibitors such as pembrolizumab[104,105]. In one study, among 6 patients with MSH2 mutations, one patient with bile duct carcinoma had a partial response (PR) and two patients with colorectal carcinoma had stable disease following treatment with pembrolizumab[104]. **Supporting Data:** Patients with mismatch repair-deficient tumors benefited from pembrolizumab in a Phase 2 study[104]: In MSI-high colorectal cancer (CRC) compared with microsatellite stable CRC, pembrolizumab demonstrated a significantly higher ORR (4/10 vs. 0/18) and disease control rate (9/10 vs. 2/18) and associated with lower risk of disease progression or death (hazard ratio 0.10); similar response rates were observed in patients with MSI-high non-CRC tumors (ORR 5/7)[104].

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

CLINICAL TRIALS TO CONSIDER

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***BRCA1*** K654fs*47	Tumors with BRCA1 inactivating mutation or loss may be sensitive to PARP inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "BRCA1", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "colorectal adenocarcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients With gBRCA Mutation Ovarian Cancer or Other Solid Tumor	Phase 1/Phase 2	PARP	Tennessee, England (United Kingdom), Scotland (United Kingdom)	NCT01482715
A Phase I Dose-Escalation Study of Oral ABT-888 (NSC #737664) Plus Intravenous Irinotecan (CPT-11, NSC#616348) Administered in Patients With Advanced Solid Tumors	Phase 1	PARP, TOP1	Connecticut, Maryland, Massachusetts, Michigan, Tennessee	NCT00576654
Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	Phase 1	CDK1, CDK2, CDK5, CDK9, PARP	Massachusetts	NCT01434316
Pilot Trial of BMN 673, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations	Phase 1/Phase 2	PARP	Maryland	NCT01989546

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***BRCA2*** D946fs*14	BRCA2 loss or inactivating mutations result in accumulation of DNA damage and loss of cell cycle control, and may predict sensitivity to inhibitors of PARP, which facilitates DNA repair. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "BRCA2", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "colorectal carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients With gBRCA Mutation Ovarian Cancer or Other Solid Tumor	Phase 1/Phase 2	PARP	Tennessee, England (United Kingdom), Scotland (United Kingdom)	NCT01482715
Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	Phase 1	CDK1, CDK2, CDK5, CDK9, PARP	Massachusetts	NCT01434316
A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.	Phase 1	PARP, PD-L1, ATR	California, New York, London (United Kingdom), Manchester (United Kingdom), Seoul (Korea, Republic of), Sutton (United Kingdom), Villejuif (France)	NCT02264678
Pilot Trial of BMN 673, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations	Phase 1/Phase 2	PARP	Maryland	NCT01989546
A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours	Phase 1	AKT, PARP	Newcastle upon Tyne (United Kingdom), Surrey (United Kingdom)	NCT02338622

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***HRAS*** G12S	HRAS amplification or activating mutations may result in activation of the RAF-MEK-ERK and PI3K-AKT pathways, and may therefore predict sensitivity to MEK and PI3K inhibitors. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required for efficacy. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "RAS", "MEK", "PI3K", "trametinib", "cobimetinib", "reolysin", "colorectal carcinoma", and/or "solid tumor".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase Ib Open-label, Multi-center, Dose Escalation and Expansion Study of Orally Administered MEK162 Plus BYL719 in Adult Patients With Selected Advanced Solid Tumors	Phase 1/Phase 2	PI3K-alpha, MEK	Illinois, Massachusetts, New York	NCT01449058
A Cancer Research UK Phase I Dose Escalation Trial of Oral VEGFR and EGFR Inhibitor, Vandetanib in Combination With the Oral MEK Inhibitor, Selumetinib (VanSel-1) in Solid Tumours (Dose Escalation) and NSCLC (Expansion Cohort).	Phase 1	MEK, RET, VEGFR2, EGFR	Cambridge (United Kingdom), Manchester (United Kingdom), Newcastle (United Kingdom), Oxford (United Kingdom)	NCT01586624
A Phase 1b, Multi-center, Open-label, Dose Escalation Study of GSK2256098 (FAK Inhibitor) in Combination With Trametinib (MEK Inhibitor) in Subjects With Advanced Solid Tumors	Phase 1	MEK, FAK	London (United Kingdom)	NCT01938443
A Phase IB Study of the Combination of AZD6244 Hydrogen Sulfate (Selumetinib) and Cyclosporin A (CsA) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Colorectal Cancer	Phase 1	MEK	Colorado, Missouri, New Jersey, North Carolina, Ohio, Pennsylvania, Texas, Ontario (Canada)	NCT02188264

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***MSH2*** G71*	Inactivation of MSH2 may lead to microsatellite instability and may therefore confer sensitivity to anti-PD-1 immune checkpoint inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "PD-1", "pembrolizumab", "nivolumab", "colorectal carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab in Subjects With Advanced or Metastatic Solid Tumors	Phase 1/Phase 2	PD-1, CTLA-4	Colorado, Connecticut, Florida, Georgia, Maryland, Massachusetts, New York, North Carolina, Oregon, Tennessee, Texas, Washington, Barcelona (Spain), Bonn (Germany), Frankfurt (Germany), Greater London (United Kingdom), Heidelberg (Germany), Helsinki (Finland), K?benhavn ? (Denmark), Lanarkshire (United Kingdom), Madrid (Spain), Milano (Italy), Napoli (Italy), Ontario (Canada), Surrey (United Kingdom), Tampere (Finland)	NCT01928394
A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors	Phase 1	LAG-3, PD-1	Illinois, Maryland, Massachusetts, New York, Oregon, Barcelona (Spain), Pamplona (Spain)	NCT01968109
A Phase 1 Trial of MK-3475 Plus Ziv-Aflibercept in Patients With Advanced Solid Tumors	Phase 1	PD-1, VEGF-A, VEGF-B, PIGF	Florida, Massachusetts, Ontario (Canada)	NCT02298959
A Phase Ib/II Study of Pembrolizumab and Monoclonal Antibody Therapy in Patients With Advanced Cancer (PembroMab	Phase 1/Phase 2	PD-1, EGFR, ERBB2	Arizona	NCT02318901
A Multi-Center, Single Arm, Phase II Study of Pembrolizumab (MK-3475) in Combination With Chemotherapy for Patients With Advanced Colorectal Cancer: HCRN GI14-186	Phase 2	PD-1	Georgia, Indiana, Ohio	NCT02375672
A First-in-Human Study of Repeat Dosing With REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death - 1 (PD 1), as Single Therapy and in Combination With Other Anti-Cancer Therapies in Patients With Advanced Malignancies	Phase 1	PD-1	Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Massachusetts, Missouri, New Jersey, New York, North Carolina, Ohio,	NCT02383212

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			Oklahoma, Oregon, Pennsylvania, Tennessee, Texas, Barcelona (Spain), Madrid (Spain)	
A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite High (MSI-H) Colon Cancer	Phase 1/Phase 2	PD-1, CTLA-4	Arizona, California, Georgia, Massachusetts, Minnesota, North Carolina, Oregon, Pennsylvania, Tennessee, Texas, Alberta (Canada), Brussels (Belgium), Dublin 4 (Ireland), Dublin 9 (Ireland), Galway (Ireland), Leuven (Belgium), Madrid (Spain), Modena (Italy), New South Wales (Australia), Ontario (Canada), Padova (Italy), Paris (France), Queensland (Australia), Sevilla (Spain), TO (Italy), Victoria (Australia)	NCT02060188
A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI0680 (AMP-514) in Combination With MEDI4736 in Subjects With Advanced Malignancies	Phase 1/Phase 2	PD-1, PD-L1	California, Florida, New Jersey, New York, Oregon, South Carolina, Washington	NCT02118337

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***ATM*** N2586fs*20	Loss or inactivation of ATM may increase sensitivity to PARP inhibitors or inhibitors of DNA-PKcs. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "DNA-PK", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "colorectal cancer", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	Phase 1	CDK1, CDK2, CDK5, CDK9, PARP	Massachusetts	NCT01434316
An Early Phase 1 Study of ABT-888 in Combination With Carboplatin and Paclitaxel in Patients With Hepatic or Renal Dysfunction and Solid Tumors	Phase 1	PARP	California, Maryland, Massachusetts, Michigan, New Jersey, New York, Pennsylvania, Texas, Wisconsin	NCT01366144
A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours	Phase 1	AKT, PARP	Newcastle upon Tyne (United Kingdom), Surrey (United Kingdom)	NCT02338622
A Multicenter, Open-Label, Dose-Escalating Phase I Trial of the DNA-PK Inhibitor MSC2490484A in Subjects With Advanced Solid Tumors or Chronic Lymphocytic Leukemia	Phase 1	DNA-PK	Darmstadt (Germany)	NCT02316197
A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.	Phase 1	PARP, PD-L1, ATR	California, New York, London (United Kingdom), Manchester (United Kingdom), Seoul (Korea, Republic of), Sutton (United Kingdom), Villejuif (France)	NCT02264678

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***CTNNB1*** T41I	Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors. However, several clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies for the treatment of colorectal cancer; combinations of therapies may be required to overcome this lack of response. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "mTOR", "everolimus", "temsirolimus", "GDC-0980", "GSK2126458", "PF-04691502", "PF-05212384", "INK-128", "OSI-027", "CC-223", "DS-3078a", "colorectal carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors	Phase 1	mTORC1, mTORC2, VEGFA	Massachusetts	NCT02142803
A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	mTORC1, mTORC2	Florida, Oklahoma, Tennessee	NCT02412722
A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	PI3K-alpha, mTORC1, mTORC2	Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)	NCT01899053
TAX-TORC: A Phase I Multi-centre Trial of the Combination of AZD2014 (Dual mTORC1 and mTORC2 Inhibitor) and Weekly Paclitaxel in Patients With Solid Tumours.	Phase 1	mTORC1, mTORC2	Cambridgeshire (United Kingdom), London (United Kingdom), Surrey (United Kingdom)	NCT02193633

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***FBXW7*** R479Q	FBXW7 inactivation may lead to increased mTOR activation, and may therefore predict sensitivity to mTOR inhibitors. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required for efficacy. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "mTOR", "everolimus", "temsirolimus", "colorectal carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	PI3K-alpha, mTORC1, mTORC2	Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)	NCT01899053
TAX-TORC: A Phase I Multi-centre Trial of the Combination of AZD2014 (Dual mTORC1 and mTORC2 Inhibitor) and Weekly Paclitaxel in Patients With Solid Tumours.	Phase 1	mTORC1, mTORC2	Cambridgeshire (United Kingdom), London (United Kingdom), Surrey (United Kingdom)	NCT02193633
A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors	Phase 1	mTORC1, mTORC2, VEGFA	Massachusetts	NCT02142803
A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	mTORC1, mTORC2, RAF, Aurora kinase A	Massachusetts, Pennsylvania, Barcelona (Spain), Oxfordshire (United Kingdom)	NCT02327169

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***RNF43*** G659fs*41, R225fs*194	Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "beta catenin", "WNT", "DKK1", "DKK3, "SFRP1", "calcimycin", "PRI-724", "ETC-1922159", "colorectal carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1A/B Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours	Phase 1	PORCN	Texas	NCT02521844

APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

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 make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

AKT2
R357H

ALK
W915fs*24

ATR
L594F

AXL
P586H

BARD1
P358_S364del

BRCA2
G1963V

CCND2
G268R

CHEK2
L193P

CIC
A1554T

CTNNB1
R200H

DNMT3A
R749H,V510I

EPHA7
R6W

EPHB1
A318E

ERBB3
R1127C

FANCA
I699V,R435C

FANCD2
splice site 990-1G>A

FAT1
I3448del

FBXW7
F45C

FGFR3
A281T

FLT3
V819fs*11

GLI1
G274fs*6

GPR124
P550S,R362H,R911Q

IDH1
R20Q

IKZF1
P279S

KDR
R57T

KEAP1
D294N

LMO1
R105W

LRP1B
V4264I

MLL
S729del

MLL3
N2842fs*2

MTOR
R1482C

NOTCH2
M1I

PBRM1
R598K

PIK3C2B
L1293P

PIK3CB
I1021M

PLCG2
P442T

PTPN11
T397M

ROS1
R118*

SDHA
A442T

SF3B1
R124W

SLIT2
R726H

SMO
P694fs*82

SPTA1
L1977P

SYK
G618E

TGFBR2
F186del

TSC2
R680Q

APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all 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 315 genes as well as introns of 28 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	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

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APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99.0% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Specificity of all variant types	Positive Predictive Value (PPV)	>99.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision

*95% Confidence Interval

** Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

[1] Based on analysis of coverage and re-arrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.

[2] Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. et al. Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

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

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

APPENDIX

REFERENCES

1 O'Donovan PJ, Livingston DM (2010) BRCA1 and BRCA2: breast/ovarian cancer susceptibility gene products and participants in DNA double-strand break repair. Carcinogenesis 31(6):961-7.

2 Nelson AC, Holt JT (2010) Impact of RING and BRCT domain mutations on BRCA1 protein stability, localization and recruitment to DNA damage. Radiat Res 174(1):1-13.

3 Silver DP, Livingston DM (2012) Mechanisms of BRCA1 tumor suppression. Cancer Discov 2(8):679-84.

4 Ludwig T, Fisher P, Ganesan S, et al. (2001) Tumorigenesis in mice carrying a truncating Brca1 mutation. Genes Dev 15(10):1188-93.

5 Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266(5182):66-71.

6 Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 378(6559):789-92.

7 Ford D, Easton DF, Bishop DT, et al. (1994) Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 343(8899):692-5.

8 Friedenson B (2005) BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed 7(2):60.

9 Whittemore AS, Gong G, Itnyre J (1997) Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 60(3):496-504.

10 Claus EB, Schildkraut JM, Thompson WD, et al. (1996) The genetic attributable risk of breast and ovarian cancer. Cancer 77(11):2318-24.

11 Struewing JP, Hartge P, Wacholder S, et al. (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336(20):1401-8.

12 Oddoux C, Struewing JP, Clayton CM, et al. (1996) The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet 14(2):188-90.

13 King MC, Marks JH, Mandell JB, et al. (2003) Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302(5645):643-6.

14 Hall MJ, Reid JE, Burbidge LA, et al. (2009) BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer 115(10):2222-33.

15 Cancer Genome Atlas Network (2012) Comprehensive molecular characterization of human colon and rectal cancer. Nature 487(7407):330-7.

16 Grabsch H, Dattani M, Barker L, et al. (2006) Expression of DNA double-strand break repair proteins ATM and BRCA1 predicts survival in colorectal cancer. Clin Cancer Res 12(5):1494-500.

17 Suchy J, Cybulski C, Górski B, et al. (2010) BRCA1 mutations and colorectal cancer in Poland. Fam Cancer 9(4):541-4.

18 Kadouri L, Hubert A, Rotenberg Y, et al. (2007) Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. J Med Genet 44(7):467-71.

19 Alli E, Sharma VB, Hartman AR, et al. (2011) Enhanced sensitivity to cisplatin and gemcitabine in Brca1-deficient murine mammary epithelial cells. BMC Pharmacol 11:7.

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APPENDIX

REFERENCES

[20] Rottenberg S, Jaspers JE, Kersbergen A, et al. (2008) High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci USA 105(44):17079-84.

[21] Byrski T, Huzarski T, Dent R, et al. (2009) Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 115(2):359-63.

[22] Imyanitov EN, Byrski T (2013) Systemic treatment for hereditary cancers: a 2012 update. Hered Cancer Clin Pract 11(1):2.

[23] Yang H, Jeffrey PD, Miller J, et al. (2002) BRCA2 function in DNA binding and recombination from a BRCA2-DSS1-ssDNA structure. Science 297(5588):1837-48.

[24] Holloman WK (2011) Unraveling the mechanism of BRCA2 in homologous recombination. Nat Struct Mol Biol 18(7):748-54.

[25] Al Abo M, Dejsuphong D, Hirota K, et al. (2014) Compensatory functions and interdependency of the DNA-binding domain of BRCA2 with the BRCA1-PALB2-BRCA2 complex. Cancer Res 74(3):797-807.

[26] Biswas K, Das R, Alter BP, et al. (2011) A comprehensive functional characterization of BRCA2 variants associated with Fanconi anemia using mouse ES cell-based assay. Blood 118(9):2430-42.

[27] Claes K, Poppe B, Coene I, et al. (2004) BRCA1 and BRCA2 germline mutation spectrum and frequencies in Belgian breast/ovarian cancer families. Br J Cancer 90(6):1244-51.

[28] Farrugia DJ, Agarwal MK, Pankratz VS, et al. (2008) Functional assays for classification of BRCA2 variants of uncertain significance. Cancer Res 68(9):3523-31.

[29] Gómez García EB, Oosterwijk JC, Timmermans M, et al. (2009) A method to assess the clinical significance of unclassified variants in the BRCA1 and BRCA2 genes based on cancer family history. Breast Cancer Res 11(1):R8.

[30] Guidugli L, Pankratz VS, Singh N, et al. (2013) A classification model for BRCA2 DNA binding domain missense variants based on homology-directed repair activity. Cancer Res 73(1):265-75.

[31] Kuznetsov SG, Liu P, Sharan SK (2008) Mouse embryonic stem cell-based functional assay to evaluate mutations in BRCA2. Nat Med 14(8):875-81.

[32] Roy R, Chun J, Powell SN (2012) BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer 12(1):68-78.

[33] Siaud N, Barbera MA, Egashira A, et al. (2011) Plasticity of BRCA2 function in homologous recombination: genetic interactions of the PALB2 and DNA binding domains. PLoS Genet 7(12):e1002409.

[34] Thomassen M, Kruse TA, Jensen PK, et al. (2006) A missense mutation in exon 13 in BRCA2, c.7235G>A, results in skipping of exon 13. Genet Test 10(2):116-20.

[35] Biswas K, Das R, Eggington JM, et al. (2012) Functional evaluation of BRCA2 variants mapping to the PALB2-binding and C-terminal DNA-binding domains using a mouse ES cell-based assay. Hum Mol Genet 21(18):3993-4006.

[36] Cote S, Arcand SL, Royer R, et al. (2012) The BRCA2 c.9004G>A (E2002K) [corrected] variant is likely pathogenic and recurs in breast and/or ovarian cancer families of French Canadian descent. Breast Cancer Res Treat 131(1):333-40.

[37] Xia B, Sheng Q, Nakanishi K, et al. (2006) Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell 22(6):719-29.

[38] Kluska A, Balabas A, Paziewska A, et al. (2015) New recurrent BRCA1/2 mutations in Polish patients with familial breast/ovarian cancer detected by next generation sequencing. BMC Med Genomics 8:19.

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APPENDIX

REFERENCES

[39] Bougie O, Weberpals JI (2011) Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review. Int J Surg Oncol 2011:374012.

[40] Breast Cancer Linkage Consortium (1999) Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91(15):1310-6.

[41] Hahn SA, Greenhalf B, Ellis I, et al. (2003) BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 95(3):214-21.

[42] Monnerat C, Chompret A, Kannengiesser C, et al. (2007) BRCA1, BRCA2, TP53, and CDKN2A germline mutations in patients with breast cancer and cutaneous melanoma. Fam Cancer 6(4):453-61.

[43] Casula M, Muggiano A, Cossu A, et al. (2009) Role of key-regulator genes in melanoma susceptibility and pathogenesis among patients from South Italy. BMC Cancer 9:352.

[44] Moran A, O'Hara C, Khan S, et al. (2012) Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 11(2):235-42.

[45] Rios J, Puhalla S (2011) PARP inhibitors in breast cancer: BRCA and beyond. Oncology (Williston Park, NY) 25(11):1014-25.

[46] Fong PC, Boss DS, Yap TA, et al. (2009) Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361(2):123-34.

[47] Audeh MW, Carmichael J, Penson RT, et al. (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 376(9737):245-51.

[48] Fong PC, Yap TA, Boss DS, et al. (2010) Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 28(15):2512-9.

[49] Gelmon KA, Tischkowitz M, Mackay H, et al. (2011) Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 12(9):852-61.

[50] Kaye SB, Lubinski J, Matulonis U, et al. (2012) Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 30(4):372-9.

[51] Tutt A, Robson M, Garber JE, et al. (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 376(9737):235-44.

[52] Del Conte G, Sessa C, von Moos R, et al. (2014) Phase I study of olaparib in combination with liposomal doxorubicin in patients with advanced solid tumours. Br J Cancer 111(4):651-9.

[53] Kummar S, Chen A, Parchment RE, et al. (2012) Advances in using PARP inhibitors to treat cancer. BMC Med 10:25.

[54] Ledermann J, Harter P, Gourley C, et al. (2014) Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 15(8):852-61.

[55] Liu JF, Barry WT, Birrer M, et al. (2014) Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 15(11):1207-14.

[56] Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D (2011) RAS oncogenes: weaving a tumorigenic web. Nat Rev Cancer 11(11):761-74.

APPENDIX

REFERENCES

57 Baker R, Wilkerson EM, Sumita K, et al. (2013) Differences in the regulation of K-Ras and H-Ras isoforms by monoubiquitination. J Biol Chem 288(52):36856-62.

58 Buhrman G, Holzapfel G, Fetics S, et al. (2010) Allosteric modulation of Ras positions Q61 for a direct role in catalysis. Proc Natl Acad Sci USA 107(11):4931-6.

59 Denayer E, Parret A, Chmara M, et al. (2008) Mutation analysis in Costello syndrome: functional and structural characterization of the HRAS p.Lys117Arg mutation. Hum Mutat 29(2):232-9.

60 Fasano O, Aldrich T, Tamanoi F, et al. (1984) Analysis of the transforming potential of the human H-ras gene by random mutagenesis. Proc Natl Acad Sci USA 81(13):4008-12.

61 Feig LA, Cooper GM (1988) Relationship among guanine nucleotide exchange, GTP hydrolysis, and transforming potential of mutated ras proteins. Mol Cell Biol 8(6):2472-8.

62 Janakiraman M, Vakiani E, Zeng Z, et al. (2010) Genomic and biological characterization of exon 4 KRAS mutations in human cancer. Cancer Res 70(14):5901-11.

63 Privé GG, Milburn MV, Tong L, et al. (1992) X-ray crystal structures of transforming p21 ras mutants suggest a transition-state stabilization mechanism for GTP hydrolysis. Proc Natl Acad Sci USA 89(8):3649-53.

64 Scheffzek K, Ahmadian MR, Kabsch W, et al. (1997) The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science 277(5324):333-8.

65 Stephen AG, Esposito D, Bagni RK, et al. (2014) Dragging ras back in the ring. Cancer Cell 25(3):272-81.

66 Lea IA, Jackson MA, Dunnick JK (2009) Genetic pathways to colorectal cancer. Mutat Res 670(1-2):96-8.

67 Chen HB, Liu DX, Wang L, et al. (2010) [Immunoreactivity of monoclonal anti-p21Ras antibody KGH-R1 in colorectal benign and malignant lesions]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 26(12):1206-9.

68 Rosenberger G, Meien S, Kutsche K (2009) Oncogenic HRAS mutations cause prolonged PI3K signaling in response to epidermal growth factor in fibroblasts of patients with Costello syndrome. Hum Mutat 30(3):352-62.

69 Rosseland CM, Wierød L, Flinder LI, et al. (2008) Distinct functions of H-Ras and K-Ras in proliferation and survival of primary hepatocytes due to selective activation of ERK and PI3K. J Cell Physiol 215(3):818-26.

70 Larkin J, Ascierto PA, Dréno B, et al. (2014) Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. N Engl J Med ePub Sep 2014.

71 Flaherty KT, Robert C, Hersey P, et al. (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367(2):107-14.

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

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

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

75 Forsyth P, Roldán G, George D, et al. (2008) A phase I trial of intratumoral administration of reovirus in patients with histologically confirmed recurrent malignant gliomas. Mol Ther 16(3):627-32.

APPENDIX

REFERENCES

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

77 Gollamudi R, Ghalib MH, Desai KK, et al. (2010) Intravenous administration of Reolysin, a live replication competent RNA virus is safe in patients with advanced solid tumors. Invest New Drugs 28(5):641-9.

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

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

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

81 Galanis E, Markovic SN, Suman VJ, et al. (2012) Phase II trial of intravenous administration of Reolysin(®) (Reovirus Serotype-3-dearing Strain) in patients with metastatic melanoma. Mol Ther 20(10):1998-2003.

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

83 Morris DG, Feng X, DiFrancesco LM, et al. (2013) REO-001: A phase I trial of percutaneous intralesional administration of reovirus type 3 dearing (Reolysin®) in patients with advanced solid tumors. Invest New Drugs 31(3):696-706.

84 Peeters M, Oliner KS, Parker A, et al. (2013) Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. Clin Cancer Res 19(7):1902-12.

85 Douillard JY, Oliner KS, Siena S, et al. (2013) Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 369(11):1023-34.

86 Di Bartolomeo M, Pietrantonio F, Perrone F, et al. (2013) Lack of KRAS, NRAS, BRAF and TP53 mutations improves outcome of elderly metastatic colorectal cancer patients treated with cetuximab, oxaliplatin and UFT. Target Oncol ePub Jul 2013.

87 De Roock W, Claes B, Bernasconi D, et al. (2010) Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 11(8):753-62.

88 Kasper S, Breitenbuecher F, Reis H, et al. (2013) Oncogenic RAS simultaneously protects against anti-EGFR antibody-dependent cellular cytotoxicity and EGFR signaling blockade. Oncogene 32(23):2873-81.

89 You JF, Buhard O, Ligtenberg MJ, et al. (2010) Tumours with loss of MSH6 expression are MSI-H when screened with a pentaplex of five mononucleotide repeats. Br J Cancer 103(12):1840-5.

90 Lynch HT, Lynch PM, Lanspa SJ, et al. (2009) Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 76(1):1-18.

91 Pande M, Wei C, Chen J, et al. (2012) Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. Fam Cancer 11(3):441-7.

92 Stewart A (2013) Genetic Testing Strategies in Newly Diagnosed Endometrial Cancer Patients Aimed at Reducing Morbidity or Mortality from Lynch Syndrome in the Index Case or Her Relatives. PLoS Curr 5.

APPENDIX

REFERENCES

[93] Zhang R, Qin W, Xu GL, et al. (2012) A meta-analysis of the prevalence of somatic mutations in the hMLH1 and hMSH2 genes in colorectal cancer. Colorectal Dis 14(3):e80-9.

[94] Abdul Murad NA, Othman Z, Khalid M, et al. (2012) Missense mutations in MLH1, MSH2, KRAS, and APC genes in colorectal cancer patients in Malaysia. Dig Dis Sci 57(11):2863-72.

[95] García-Solano J, Conesa-Zamora P, Carbonell P, et al. (2012) Colorectal serrated adenocarcinoma shows a different profile of oncogene mutations, MSI status and DNA repair protein expression compared to conventional and sporadic MSI-H carcinomas. Int J Cancer 131(8):1790-9.

[96] Alkhalidi H, Kfoury H (2012) Status of mismatch repair genes hMSH2 and hMSH6 in colorectal cancer in Saudi patients: an immunohistochemical analysis. East Mediterr Health J 18(11):1114-7.

[97] Johannsdottir JT, Bergthorsson JT, Gretarsdottir S, et al. Replication error in colorectal carcinoma: association with loss of heterozygosity at mismatch repair loci and clinicopathological variables. Anticancer Res 19(3A):1821-6.

[98] Dowty JG, Win AK, Buchanan DD, et al. (2013) Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat 34(3):490-7.

[99] Mensenkamp AR, Vogelaar IP, van Zelst-Stams WA, et al. (2014) Somatic Mutations in MLH1 and MSH2 Are a Frequent Cause of Mismatch-Repair Deficiency in Lynch Syndrome-Like Tumors. Gastroenterology 146(3):643-646.e8.

[100] Joly MO, Attignon V, Saurin JC, et al. (2015) Somatic MMR gene mutations as a cause for MSI-H sebaceous neoplasms in Muir-Torre syndrome-like patients. Hum Mutat 36(3):292-5.

[101] Pritchard CC, Morrissey C, Kumar A, et al. (2014) Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun 5:4988.

[102] Rosty C, Walsh MD, Lindor NM, et al. (2014) High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry. Fam Cancer 13(4):573-82.

[103] McConechy MK, Talhouk A, Li-Chang HH, et al. (2015) Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol 137(2):306-10.

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

[105] Rizvi NA, Hellmann MD, Snyder A, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230):124-8.

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

[107] Gatalica Z, Snyder C, Maney T, et al. (2014) Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomarkers Prev 23(12):2965-70.

[108] Martin SA, McCarthy A, Barber LJ, et al. (2009) Methotrexate induces oxidative DNA damage and is selectively lethal to tumour cells with defects in the DNA mismatch repair gene MSH2. EMBO Mol Med 1(6-7):323-37.

[109] Kamal NS, Soria JC, Mendiboure J, et al. (2010) MutS homologue 2 and the long-term benefit of adjuvant chemotherapy in lung cancer. Clin Cancer Res 16(4):1206-15.

APPENDIX

REFERENCES

[110] Pierceall WE, Olaussen KA, Rousseau V, et al. (2012) Cisplatin benefit is predicted by immunohistochemical analysis of DNA repair proteins in squamous cell carcinoma but not adenocarcinoma: theranostic modeling by NSCLC constituent histological subclasses. Ann Oncol 23(9):2245-52.

[111] Shiloh Y, Ziv Y (2013) The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat Rev Mol Cell Biol 14(4):197-210.

[112] Cremona CA, Behrens A (2014) ATM signalling and cancer. Oncogene 33(26):3351-60.

[113] Jiang X, Sun Y, Chen S, et al. (2006) The FATC domains of PIKK proteins are functionally equivalent and participate in the Tip60-dependent activation of DNA-PKcs and ATM. J Biol Chem 281(23):15741-6.

[114] Uhrhammer N, Bay J, Pernin D, et al. Loss of heterozygosity at the ATM locus in colorectal carcinoma. Oncol Rep 6(3):655-8.

[115] Michels J, Vitale I, Saparbaev M, et al. (2014) Predictive biomarkers for cancer therapy with PARP inhibitors. Oncogene 33(30):3894-907.

[116] Weston VJ, Oldreive CE, Skowronska A, et al. (2010) The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo. Blood 116(22):4578-87.

[117] Williamson CT, Muzik H, Turhan AG, et al. (2010) ATM deficiency sensitizes mantle cell lymphoma cells to poly(ADP-ribose) polymerase-1 inhibitors. Mol Cancer Ther 9(2):347-57.

[118] Gilardini Montani MS, Prodosmo A, Stagni V, et al. (2013) ATM-depletion in breast cancer cells confers sensitivity to PARP inhibition. J Exp Clin Cancer Res 32:95.

[119] Bryant HE, Helleday T (2006) Inhibition of poly (ADP-ribose) polymerase activates ATM which is required for subsequent homologous recombination repair. Nucleic Acids Res 34(6):1685-91.

[120] Ihnen M, zu Eulenburg C, Kolarova T, et al. (2013) Therapeutic potential of the poly(ADP-ribose) polymerase inhibitor rucaparib for the treatment of sporadic human ovarian cancer. Mol Cancer Ther 12(6):1002-15.

[121] Williamson CT, Kubota E, Hamill JD, et al. (2012) Enhanced cytotoxicity of PARP inhibition in mantle cell lymphoma harbouring mutations in both ATM and p53. EMBO Mol Med 4(6):515-27.

[122] Kubota E, Williamson CT, Ye R, et al. (2014) Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. Cell Cycle 13(13):2129-37.

[123] Huehls AM, Wagner JM, Huntoon CJ, et al. (2012) Identification of DNA repair pathways that affect the survival of ovarian cancer cells treated with a poly(ADP-ribose) polymerase inhibitor in a novel drug combination. Mol Pharmacol 82(4):767-76.

[124] Mateo J, Carreira S, Sandhu S, et al. (2015) DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 373(18):1697-708.

[125] Bang YJ, Im SA, Lee KW, et al. (2015) Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer. J Clin Oncol 33(33):3858-65.

[126] Riabinska A, Daheim M, Herter-Sprie GS, et al. (2013) Therapeutic targeting of a robust non-oncogene addiction to PRKDC in ATM-defective tumors. Sci Transl Med 5(189):189ra78.

[127] Kikuchi A (2000) Regulation of beta-catenin signaling in the Wnt pathway. Biochem Biophys Res Commun 268(2):243-8.

[128] Anastas JN, Moon RT (2013) WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer 13(1):11-26.

APPENDIX

REFERENCES

[129] Fukuchi T, Sakamoto M, Tsuda H, et al. (1998) Beta-catenin mutation in carcinoma of the uterine endometrium. Cancer Res 58(16):3526-8.

[130] Kikuchi A (2003) Tumor formation by genetic mutations in the components of the Wnt signaling pathway. Cancer Sci 94(3):225-9.

[131] Takahashi Y, Hiraoka N, Onozato K, et al. (2006) Solid-pseudopapillary neoplasms of the pancreas in men and women: do they differ? Virchows Arch 448(5):561-9.

[132] Tanaka Y, Kato K, Notohara K, et al. (2001) Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm. Cancer Res 61(23):8401-4.

[133] Abraham SC, Klimstra DS, Wilentz RE, et al. (2002) Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 160(4):1361-9.

[134] Austinat M, Dunsch R, Wittekind C, et al. (2008) Correlation between beta-catenin mutations and expression of Wnt-signaling target genes in hepatocellular carcinoma. Mol Cancer 7:21.

[135] Wu G, Xu G, Schulman BA, et al. (2003) Structure of a beta-TrCP1-Skp1-beta-catenin complex: destruction motif binding and lysine specificity of the SCF(beta-TrCP1) ubiquitin ligase. Mol Cell 11(6):1445-56.

[136] Provost E, McCabe A, Stern J, et al. (2005) Functional correlates of mutation of the Asp32 and Gly34 residues of beta-catenin. Oncogene 24(16):2667-76.

[137] Polakis P (1999) The oncogenic activation of beta-catenin. Curr Opin Genet Dev 9(1):15-21.

[138] Segditsas S, Tomlinson I (2006) Colorectal cancer and genetic alterations in the Wnt pathway. Oncogene 25(57):7531-7.

[139] Barth AI, Pollack AL, Altschuler Y, et al. (1997) NH2-terminal deletion of beta-catenin results in stable colocalization of mutant beta-catenin with adenomatous polyposis coli protein and altered MDCK cell adhesion. J Cell Biol 136(3):693-706.

[140] Harada N, Tamai Y, Ishikawa T, et al. (1999) Intestinal polyposis in mice with a dominant stable mutation of the beta-catenin gene. EMBO J 18(21):5931-42.

[141] Hsu SC, Galceran J, Grosschedl R (1998) Modulation of transcriptional regulation by LEF-1 in response to Wnt-1 signaling and association with beta-catenin. Mol Cell Biol 18(8):4807-18.

[142] Breuhahn K, Singh S, Schirmacher P, et al. (2008) Large-scale N-terminal deletions but not point mutations stabilize beta-catenin in small bowel carcinomas, suggesting divergent molecular pathways of small and large intestinal carcinogenesis. J Pathol 215(3):300-7.

[143] Soon PS, McDonald KL, Robinson BG, et al. (2008) Molecular markers and the pathogenesis of adrenocortical cancer. Oncologist 13(5):548-61.

[144] Tacon LJ, Prichard RS, Soon PS, et al. (2011) Current and emerging therapies for advanced adrenocortical carcinoma. Oncologist 16(1):36-48.

[145] Simon DP, Hammer GD (2012) Adrenocortical stem and progenitor cells: implications for adrenocortical carcinoma. Mol Cell Endocrinol 351(1):2-11.

[146] Seshagiri S, Stawiski EW, Durinck S, et al. (2012) Recurrent R-spondin fusions in colon cancer. Nature 488(7413):660-4.

[147] Brannon AR, Vakiani E, Sylvester BE, et al. (2014) Comparative sequencing analysis reveals high genomic concordance between matched primary and metastatic colorectal cancer lesions. Genome Biol 15(8):454.

APPENDIX

REFERENCES

[148] Jang KY, Kim YN, Bae JS, et al. (2012) Expression of Cyclin D1 Is Associated with β-Catenin Expression and Correlates with Good Prognosis in Colorectal Adenocarcinoma. Transl Oncol 5(5):370-8.

[149] Diab A, Nikolopoulou-Stamati P, Katostaras T, et al. Expression of Smad4, E-cadherin and beta-catenin in advanced colorectal cancer: a retrospective study. J BUON 17(1):92-6.

[150] White BD, Chien AJ, Dawson DW (2012) Dysregulation of Wnt/β-catenin signaling in gastrointestinal cancers. Gastroenterology 142(2):219-32.

[151] András C, Tóth L, Molnár C, et al. (2012) Correlations between clinicopathological parameters and molecular signatures of primary tumors for patients with stage T3n0 colorectal adenocarcinomas: a single center retrospective study on 100 cases. Hepatogastroenterology 59(116):1091-7.

[152] Lee SJ, Choi SY, Kim WJ, et al. (2013) Combined aberrant expression of E-cadherin and S100A4, but not β-catenin is associated with disease-free survival and overall survival in colorectal cancer patients. Diagn Pathol 8:99.

[153] Chen Z, He X, Jia M, et al. (2013) β-catenin overexpression in the nucleus predicts progress disease and unfavourable survival in colorectal cancer: a meta-analysis. PLoS ONE 8(5):e63854.

[154] Tanwar PS, Lee HJ, Zhang L, et al. (2009) Constitutive activation of Beta-catenin in uterine stroma and smooth muscle leads to the development of mesenchymal tumors in mice. Biol Reprod 81(3):545-52.

[155] Tanwar PS, Zhang L, Kaneko-Tarui T, et al. (2011) Mammalian target of rapamycin is a therapeutic target for murine ovarian endometrioid adenocarcinomas with dysregulated Wnt/β-catenin and PTEN. PLoS ONE 6(6):e20715.

[156] Fujishita T, Aoki K, Lane HA, et al. (2008) Inhibition of the mTORC1 pathway suppresses intestinal polyp formation and reduces mortality in ApcDelta716 mice. Proc Natl Acad Sci USA 105(36):13544-9.

[157] Slomovitz BM, Jiang Y, Yates MS, et al. (2015) Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol 33(8):930-6.

[158] Bhoori S, Toffanin S, Sposito C, et al. (2010) Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: a proof of principle. J Hepatol 52(5):771-5.

[159] Kwon C, Cheng P, King IN, et al. (2011) Notch post-translationally regulates β-catenin protein in stem and progenitor cells. Nat Cell Biol 13(10):1244-51.

[160] Arcaroli JJ, Quackenbush KS, Purkey A, et al. (2013) Tumours with elevated levels of the Notch and Wnt pathways exhibit efficacy to PF-03084014, a γ-secretase inhibitor, in a preclinical colorectal explant model. Br J Cancer 109(3):667-75.

[161] Shang H, Braggio D, Lee YJ, et al. (2015) Targeting the Notch pathway: A potential therapeutic approach for desmoid tumors. Cancer 121(22):4088-96.

[162] Kode A, Manavalan JS, Mosialou I, et al. (2014) Leukaemogenesis induced by an activating β-catenin mutation in osteoblasts. Nature 506(7487):240-4.

[163] Messersmith WA, Shapiro GI, Cleary JM, et al. (2015) A Phase I, dose-finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. Clin Cancer Res 21(1):60-7.

[164] Zhu J, Zhang S, Gu L, et al. (2012) Epigenetic silencing of DKK2 and Wnt signal pathway components in human ovarian carcinoma. Carcinogenesis 33(12):2334-43.

APPENDIX

REFERENCES

[165] Kogan Y, Halevi-Tobias KE, Hochman G, et al. (2012) A new validated mathematical model of the Wnt signalling pathway predicts effective combinational therapy by sFRP and Dkk. Biochem J 444(1):115-25.

[166] Lachenmayer A, Alsinet C, Savic R, et al. (2012) Wnt-pathway activation in two molecular classes of hepatocellular carcinoma and experimental modulation by sorafenib. Clin Cancer Res 18(18):4997-5007.

[167] Welcker M, Clurman BE (2008) FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 8(2):83-93.

[168] Akhoondi S, Sun D, von der Lehr N, et al. (2007) FBXW7/hCDC4 is a general tumor suppressor in human cancer. Cancer Res 67(19):9006-12.

[169] Welcker M, Larimore EA, Swanger J, et al. (2013) Fbw7 dimerization determines the specificity and robustness of substrate degradation. Genes Dev 27(23):2531-6.

[170] Welcker M, Clurman BE (2007) Fbw7/hCDC4 dimerization regulates its substrate interactions. Cell Div 2:7.

[171] Strohmaier H, Spruck CH, Kaiser P, et al. (2001) Human F-box protein hCdc4 targets cyclin E for proteolysis and is mutated in a breast cancer cell line. Nature 413(6853):316-22.

[172] Pashkova N, Gakhar L, Winistorfer SC, et al. (2010) WD40 repeat propellers define a ubiquitin-binding domain that regulates turnover of F box proteins. Mol Cell 40(3):433-43.

[173] O'Neil J, Grim J, Strack P, et al. (2007) FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J Exp Med 204(8):1813-24.

[174] Malyukova A, Brown S, Papa R, et al. (2013) FBXW7 regulates glucocorticoid response in T-cell acute lymphoblastic leukaemia by targeting the glucocorticoid receptor for degradation. Leukemia 27(5):1053-62.

[175] Thompson BJ, Buonamici S, Sulis ML, et al. (2007) The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. J Exp Med 204(8):1825-35.

[176] Kemp Z, Rowan A, Chambers W, et al. (2005) CDC4 mutations occur in a subset of colorectal cancers but are not predicted to cause loss of function and are not associated with chromosomal instability. Cancer Res 65(24):11361-6.

[177] Rajagopalan H, Jallepalli PV, Rago C, et al. (2004) Inactivation of hCDC4 can cause chromosomal instability. Nature 428(6978):77-81.

[178] Grim JE, Knoblaugh SE, Guthrie KA, et al. (2012) Fbw7 and p53 cooperatively suppress advanced and chromosomally unstable intestinal cancer. Mol Cell Biol 32(11):2160-7.

[179] Miyaki M, Yamaguchi T, Iijima T, et al. (2009) Somatic mutations of the CDC4 (FBXW7) gene in hereditary colorectal tumors. Oncology 76(6):430-4.

[180] Iwatsuki M, Mimori K, Ishii H, et al. (2010) Loss of FBXW7, a cell cycle regulating gene, in colorectal cancer: clinical significance. Int J Cancer 126(8):1828-37.

[181] Mao JH, Kim IJ, Wu D, et al. (2008) FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression. Science 321(5895):1499-502.

[182] Wang Y, Liu Y, Lu J, et al. (2013) Rapamycin inhibits FBXW7 loss-induced epithelial-mesenchymal transition and cancer stem cell-like characteristics in colorectal cancer cells. Biochem Biophys Res Commun 434(2):352-6.

APPENDIX

REFERENCES

[183] Villaruz LC, Socinski MA (2014) Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation. Lung Cancer 83(2):300-1.

[184] Olson D, Bhalla S, Yang X, et al. (2016) Novel Use of Targeted Therapy via PARP-Inhibition in a Rare Form of Papillary Renal Cell Carcinoma: A Case Report and Literature Review. Clin Genitourin Cancer ePub Mar 2016.

[185] Jardim DL, Wheler JJ, Hess K, et al. (2014) FBXW7 Mutations in Patients with Advanced Cancers: Clinical and Molecular Characteristics and Outcomes with mTOR Inhibitors. PLoS ONE 9(2):e89388.

[186] Ng K, Tabernero J, Hwang J, et al. (2013) Phase II study of everolimus in patients with metastatic colorectal adenocarcinoma previously treated with bevacizumab-, fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens. Clin Cancer Res 19(14):3987-95.

[187] Ganesan P, Janku F, Naing A, et al. (2013) Target-based therapeutic matching in early-phase clinical trials in patients with advanced colorectal cancer and PIK3CA mutations. Mol Cancer Ther 12(12):2857-63.

[188] Janku F, Hong DS, Fu S, et al. (2014) Assessing PIK3CA and PTEN in Early-Phase Trials with PI3K/AKT/mTOR Inhibitors. Cell Rep 6(2):377-87.

[189] Gulhati P, Zaytseva YY, Valentino JD, et al. (2012) Sorafenib enhances the therapeutic efficacy of rapamycin in colorectal cancers harboring oncogenic KRAS and PIK3CA. Carcinogenesis 33(9):1782-90.

[190] Altomare I, Bendell JC, Bullock KE, et al. (2011) A phase II trial of bevacizumab plus everolimus for patients with refractory metastatic colorectal cancer. Oncologist 16(8):1131-7.

[191] Wolpin BM, Ng K, Zhu AX, et al. (2013) Multicenter phase II study of tivozanib (AV-951) and everolimus (RAD001) for patients with refractory, metastatic colorectal cancer. Oncologist 18(4):377-8.

[192] Faber AC, Coffee EM, Costa C, et al. (2014) mTOR inhibition specifically sensitizes colorectal cancers with KRAS or BRAF mutations to BCL-2/BCL-XL inhibition by suppressing MCL-1. Cancer Discov 4(1):42-52.

[193] Aydin IT, Melamed RD, Adams SJ, et al. (2014) FBXW7 mutations in melanoma and a new therapeutic paradigm. J Natl Cancer Inst 106(6):dju107.

[194] Fouladi M, Stewart CF, Olson J, et al. (2011) Phase I trial of MK-0752 in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J Clin Oncol 29(26):3529-34.

[195] Groth C, Fortini ME (2012) Therapeutic approaches to modulating Notch signaling: current challenges and future prospects. Semin Cell Dev Biol 23(4):465-72.

[196] Ganesan P, Moulder S, Lee JJ, et al. (2014) Triple Negative Breast Cancer Patients Treated at MD Anderson Cancer Center in Phase I Trials: Improved Outcomes with Combination Chemotherapy and Targeted Agents. Mol Cancer Ther ePub Sep 2014.

[197] Delmore JE, Issa GC, Lemieux ME, et al. (2011) BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 146(6):904-17.

[198] Bandopadhayay P, Bergthold G, Nguyen B, et al. (2013) BET-bromodomain inhibition of MYC-amplified Medulloblastoma. Clin Cancer Res ePub Dec 2013.

[199] Lovén J, Hoke HA, Lin CY, et al. (2013) Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell 153(2):320-34.

APPENDIX

REFERENCES

[200] Ma T, Galimberti F, Erkmen CP, et al. (2013) Comparing Histone Deacetylase Inhibitor Responses in Genetically Engineered Mouse Lung Cancer Models and a Window of Opportunity Trial in Lung Cancer Patients. Mol Cancer Ther ePub May 2013.

[201] Wertz IE, Kusam S, Lam C, et al. (2011) Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 471(7336):110-4.

[202] Sugiura T, Yamaguchi A, Miyamoto K (2008) A cancer-associated RING finger protein, RNF43, is a ubiquitin ligase that interacts with a nuclear protein, HAP95. Exp Cell Res 314(7):1519-28.

[203] Yagyu R, Furukawa Y, Lin YM, et al. (2004) A novel oncoprotein RNF43 functions in an autocrine manner in colorectal cancer. Int J Oncol 25(5):1343-8.

[204] Hao HX, Xie Y, Zhang Y, et al. (2012) ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. Nature 485(7397):195-200.

[205] Koo BK, Spit M, Jordens I, et al. (2012) Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors. Nature 488(7413):665-9.

[206] Jiang X, Hao HX, Growney JD, et al. (2013) Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. Proc Natl Acad Sci USA 110(31):12649-54.

[207] Koo BK, van Es JH, van den Born M, et al. (2015) Porcupine inhibitor suppresses paracrine Wnt-driven growth of Rnf43;Znrf3-mutant neoplasia. Proc Natl Acad Sci USA 112(24):7548-50.

[208] Tsukiyama T, Fukui A, Terai S, et al. (2015) Molecular Role of RNF43 in Canonical and Noncanonical Wnt Signaling. Mol Cell Biol 35(11):2007-23.

[209] Shinada K, Tsukiyama T, Sho T, et al. (2011) RNF43 interacts with NEDL1 and regulates p53-mediated transcription. Biochem Biophys Res Commun 404(1):143-7.

[210] Kinde I, Bettegowda C, Wang Y, et al. (2013) Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. Sci Transl Med 5(167):167ra4.

[211] Giannakis M, Hodis E, Jasmine Mu X, et al. (2014) RNF43 is frequently mutated in colorectal and endometrial cancers. Nat Genet 46(12):1264-6.

[212] Madan B, Virshup DM (2015) Targeting Wnts at the source--new mechanisms, new biomarkers, new drugs. Mol Cancer Ther 14(5):1087-94.

[213] Ryland GL, Hunter SM, Doyle MA, et al. (2013) RNF43 is a tumour suppressor gene mutated in mucinous tumours of the ovary. J Pathol 229(3):469-76.

[214] Ong CK, Subimerb C, Pairojkul C, et al. (2012) Exome sequencing of liver fluke-associated cholangiocarcinoma. Nat Genet 44(6):690-3.

[215] Wang K, Yuen ST, Xu J, et al. (2014) Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet 46(6):573-82.

[216] The Cancer Genome Atlas Research Network, Analysis Working Group: Dana-Farber Cancer Institute, Institute for Systems Biology, et al. (2014) Comprehensive molecular characterization of gastric adenocarcinoma. Nature ePub Jul 2014.

[217] Kosho T, Okamoto N, Ohashi H, et al. (2013) Clinical correlations of mutations affecting six components of the SWI/SNF complex: detailed description of 21 patients and a review of the literature. Am J Med Genet A 161A(6):1221-37.

APPENDIX

REFERENCES

[218] Shain AH, Pollack JR (2013) The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS ONE 8(1):e55119.

[219] Hunter Z, Xu L, Yang G, et al. (2013) The genomic landscape of Waldenstom's Macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood ePub Dec 2013.

[220] Cajuso T, Hänninen UA, Kondelin J, et al. (2013) Exome sequencing reveals frequent inactivating mutations in ARID1A,ARID1B,ARID2, and ARID4A in microsatellite unstable colorectal cancer. Int J Cancer ePub Dec 2013.

[221] Aso T, Uozaki H, Morita S, et al. (2015) Loss of ARID1A, ARID1B, and ARID2 Expression During Progression of Gastric Cancer. Anticancer Res 35(12):6819-27.

[222] Sausen M, Leary RJ, Jones S, et al. (2013) Integrated genomic analyses identify ARID1A and ARID1B alterations in the childhood cancer neuroblastoma. Nat Genet 45(1):12-7.

[223] Vasileiou G, Ekici AB, Uebe S, et al. (2015) Chromatin-Remodeling-Factor ARID1B Represses Wnt/β-Catenin Signaling. Am J Hum Genet 97(3):445-56.

[224] Abdel-Wahab O, Gao J, Adli M, et al. (2013) Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. J Exp Med 210(12):2641-59.

[225] Katoh M (2013) Functional and cancer genomics of ASXL family members. Br J Cancer 109(2):299-306.

[226] Hoischen A, van Bon BW, Rodríguez-Santiago B, et al. (2011) De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. Nat Genet 43(8):729-31.

[227] Inoue D, Kitaura J, Togami K, et al. (2013) Myelodysplastic syndromes are induced by histone methylation–altering ASXL1 mutations. J Clin Invest 123(11):4627-40.

[228] Abdel-Wahab O, Adli M, LaFave LM, et al. (2012) ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell 22(2):180-93.

[229] Stephens PJ, Tarpey PS, Davies H, et al. (2012) The landscape of cancer genes and mutational processes in breast cancer. Nature 486(7403):400-4.

[230] Ahn SM, Jang SJ, Shim JH, et al. (2014) A genomic portrait of resectable hepatocellular carcinomas: Implications of RB1 and FGF19 aberrations for patient stratification. Hepatology ePub May 2014.

[231] Grasso CS, Wu YM, Robinson DR, et al. (2012) The mutational landscape of lethal castration-resistant prostate cancer. Nature 487(7406):239-43.

[232] Stransky N, Egloff AM, Tward AD, et al. (2011) The mutational landscape of head and neck squamous cell carcinoma. Science 333(6046):1157-60.

[233] Scotto L, Narayan G, Nandula SV, et al. (2008) Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: potential role in progression. Genes Chromosomes Cancer 47(9):755-65.

[234] Gelsi-Boyer V, Brecqueville M, Devillier R, et al. (2012) Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. J Hematol Oncol 5:12.

[235] Rozenblatt-Rosen O, Hughes CM, Nannepaga SJ, et al. (2005) The parafibromin tumor suppressor protein is part of a human Paf1 complex. Mol Cell Biol 25(2):612-20.

APPENDIX

REFERENCES

[236] Mosimann C, Hausmann G, Basler K (2006) Parafibromin/Hyrax activates Wnt/Wg target gene transcription by direct association with beta-catenin/Armadillo. Cell 125(2):327-41.

[237] Yang YJ, Han JW, Youn HD, et al. (2010) The tumor suppressor, parafibromin, mediates histone H3 K9 methylation for cyclin D1 repression. Nucleic Acids Res 38(2):382-90.

[238] Lin L, Zhang JH, Panicker LM, et al. (2008) The parafibromin tumor suppressor protein inhibits cell proliferation by repression of the c-myc proto-oncogene. Proc Natl Acad Sci USA 105(45):17420-5.

[239] Zheng HC, Wei ZL, Xu XY, et al. (2011) Parafibromin expression is an independent prognostic factor for colorectal carcinomas. Hum Pathol 42(8):1089-102.

[240] Masi G, Iacobone M, Sinigaglia A, et al. (2014) Characterization of a new CDC73 missense mutation that impairs Parafibromin expression and nucleolar localization. PLoS ONE 9(5):e97994.

[241] Woodard GE, Lin L, Zhang JH, et al. (2005) Parafibromin, product of the hyperparathyroidism-jaw tumor syndrome gene HRPT2, regulates cyclin D1/PRAD1 expression. Oncogene 24(7):1272-6.

[242] Rather MI, Nagashri MN, Swamy SS, et al. (2013) Oncogenic microRNA-155 down-regulates tumor suppressor CDC73 and promotes oral squamous cell carcinoma cell proliferation: implications for cancer therapeutics. J Biol Chem 288(1):608-18.

[243] Rather MI, Swamy S, Gopinath KS, et al. (2014) Transcriptional repression of tumor suppressor CDC73, encoding an RNA polymerase II interactor, by Wilms tumor 1 protein (WT1) promotes cell proliferation: implication for cancer therapeutics. J Biol Chem 289(2):968-76.

[244] Zhang C, Kong D, Tan MH, et al. (2006) Parafibromin inhibits cancer cell growth and causes G1 phase arrest. Biochem Biophys Res Commun 350(1):17-24.

[245] Takahashi A, Tsutsumi R, Kikuchi I, et al. (2011) SHP2 tyrosine phosphatase converts parafibromin/Cdc73 from a tumor suppressor to an oncogenic driver. Mol Cell 43(1):45-56.

[246] James RG, Biechele TL, Conrad WH, et al. (2009) Bruton's tyrosine kinase revealed as a negative regulator of Wnt-beta-catenin signaling. Sci Signal 2(72):ra25.

[247] Carpten JD, Robbins CM, Villablanca A, et al. (2002) HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 32(4):676-80.

[248] Krebs LJ, Shattuck TM, Arnold A (2005) HRPT2 mutational analysis of typical sporadic parathyroid adenomas. J Clin Endocrinol Metab 90(9):5015-7.

[249] Shattuck TM, Välimäki S, Obara T, et al. (2003) Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med 349(18):1722-9.

[250] Cetani F, Banti C, Pardi E, et al. (2013) CDC73 mutational status and loss of parafibromin in the outcome of parathyroid cancer. Endocr Connect 2(4):186-95.

[251] Witteveen JE, Hamdy NA, Dekkers OM, et al. (2011) Downregulation of CASR expression and global loss of parafibromin staining are strong negative determinants of prognosis in parathyroid carcinoma. Mod Pathol 24(5):688-97.

[252] Gumbiner BM (2005) Regulation of cadherin-mediated adhesion in morphogenesis. Nat Rev Mol Cell Biol 6(8):622-34.

[253] Wong AS, Gumbiner BM (2003) Adhesion-independent mechanism for suppression of tumor cell invasion by E-cadherin. J Cell Biol 161(6):1191-203.

APPENDIX

REFERENCES

[254] Sarrió D, Moreno-Bueno G, Hardisson D, et al. (2003) Epigenetic and genetic alterations of APC and CDH1 genes in lobular breast cancer: relationships with abnormal E-cadherin and catenin expression and microsatellite instability. Int J Cancer 106(2):208-15.

[255] Mastracci TL, Tjan S, Bane AL, et al. (2005) E-cadherin alterations in atypical lobular hyperplasia and lobular carcinoma in situ of the breast. Mod Pathol 18(6):741-51.

[256] Berx G, van Roy F (2009) Involvement of members of the cadherin superfamily in cancer. Cold Spring Harb Perspect Biol 1(6):a003129.

[257] Shapiro L, Weis WI (2009) Structure and biochemistry of cadherins and catenins. Cold Spring Harb Perspect Biol 1(3):a003053.

[258] Shiraishi K, Tsuzaka K, Yoshimoto K, et al. (2005) Critical role of the fifth domain of E-cadherin for heterophilic adhesion with alpha E beta 7, but not for homophilic adhesion. J Immunol 175(2):1014-21.

[259] van Roy F (2014) Beyond E-cadherin: roles of other cadherin superfamily members in cancer. Nat Rev Cancer 14(2):121-34.

[260] Ishiyama N, Lee SH, Liu S, et al. (2010) Dynamic and static interactions between p120 catenin and E-cadherin regulate the stability of cell-cell adhesion. Cell 141(1):117-28.

[261] Brooks-Wilson AR, Kaurah P, Suriano G, et al. (2004) Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J Med Genet 41(7):508-17.

[262] Vogelaar IP, van der Post RS, Bisseling TM, et al. (2012) Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. Hered Cancer Clin Pract 10(1):18.

[263] Pharoah PD, Guilford P, Caldas C, et al. (2001) Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 121(6):1348-53.

[264] Fang WL, Chang SC, Lan YT, et al. (2013) Molecular and survival differences between familial and sporadic gastric cancers. Biomed Res Int 2013:396272.

[265] Benusiglio PR, Malka D, Rouleau E, et al. (2013) CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet 50(7):486-9.

[266] Schrader KA, Masciari S, Boyd N, et al. (2008) Hereditary diffuse gastric cancer: association with lobular breast cancer. Fam Cancer 7(1):73-82.

[267] Xie ZM, Li LS, Laquet C, et al. (2011) Germline mutations of the E-cadherin gene in families with inherited invasive lobular breast carcinoma but no diffuse gastric cancer. Cancer 117(14):3112-7.

[268] Petridis C, Shinomiya I, Kohut K, et al. (2013) Germline CDH1 mutations in bilateral lobular carcinoma in situ. Br J Cancer ePub Dec 2013.

[269] Makrilia N, Kollias A, Manolopoulos L, et al. (2009) Cell adhesion molecules: role and clinical significance in cancer. Cancer Invest 27(10):1023-37.

[270] Kroepil F, Fluegen G, Totikov Z, et al. (2012) Down-regulation of CDH1 is associated with expression of SNAI1 in colorectal adenomas. PLoS ONE 7(9):e46665.

[271] Lind GE, Thorstensen L, Løvig T, et al. (2004) A CpG island hypermethylation profile of primary colorectal carcinomas and colon cancer cell lines. Mol Cancer 3:28.

[272] Xu XL, Yu J, Zhang HY, et al. (2004) Methylation profile of the promoter CpG islands of 31 genes that may contribute to colorectal carcinogenesis. World J Gastroenterol 10(23):3441-54.

APPENDIX

REFERENCES

[273] Ding J, Zhang ZM, Xia Y, et al. (2013) LSD1-mediated epigenetic modification contributes to proliferation and metastasis of colon cancer. Br J Cancer 109(4):994-1003.

[274] Pittman AM, Twiss P, Broderick P, et al. (2009) The CDH1-160C>A polymorphism is a risk factor for colorectal cancer. Int J Cancer 125(7):1622-5.

[275] Zlobec I, Lugli A, Baker K, et al. (2007) Role of APAF-1, E-cadherin and peritumoral lymphocytic infiltration in tumour budding in colorectal cancer. J Pathol 212(3):260-8.

[276] Buda A, Pignatelli M (2004) Cytoskeletal network in colon cancer: from genes to clinical application. Int J Biochem Cell Biol 36(5):759-65.

[277] Matsuoka T, Mitomi H, Fukui N, et al. (2011) Cluster analysis of claudin-1 and -4, E-cadherin, and β-catenin expression in colorectal cancers. J Surg Oncol 103(7):674-86.

[278] Karamitopoulou E, Zlobec I, Patsouris E, et al. (2011) Loss of E-cadherin independently predicts the lymph node status in colorectal cancer. Pathology 43(2):133-7.

[279] Capelli LP, Krepischi AC, Gurgel-Giannetti J, et al. (2012) Deletion of the RMGA and CHD2 genes in a child with epilepsy and mental deficiency. Eur J Med Genet 55(2):132-4.

[280] Suls A, Jaehn JA, Kecskés A, et al. (2013) De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. Am J Hum Genet 93(5):967-75.

[281] Lund C, Brodtkorb E, Øye AM, et al. (2014) CHD2 mutations in Lennox-Gastaut syndrome. Epilepsy Behav 33:18-21.

[282] Kim MS, Chung NG, Kang MR, et al. (2011) Genetic and expressional alterations of CHD genes in gastric and colorectal cancers. Histopathology 58(5):660-8.

[283] Bandrés E, Malumbres R, Cubedo E, et al. (2007) A gene signature of 8 genes could identify the risk of recurrence and progression in Dukes' B colon cancer patients. Oncol Rep 17(5):1089-94.

[284] Feys T, Poppe B, De Preter K, et al. (2007) A detailed inventory of DNA copy number alterations in four commonly used Hodgkin's lymphoma cell lines. Haematologica 92(7):913-20.

[285] Nagarajan P, Onami TM, Rajagopalan S, et al. (2009) Role of chromodomain helicase DNA-binding protein 2 in DNA damage response signaling and tumorigenesis. Oncogene 28(8):1053-62.

[286] Ramírez J, Hagman J (2009) The Mi-2/NuRD complex: a critical epigenetic regulator of hematopoietic development, differentiation and cancer. Epigenetics 4(8):532-6.

[287] Lai AY, Wade PA (2011) Cancer biology and NuRD: a multifaceted chromatin remodelling complex. Nat Rev Cancer 11(8):588-96.

[288] Cai Y, Geutjes EJ, de Lint K, et al. (2014) The NuRD complex cooperates with DNMTs to maintain silencing of key colorectal tumor suppressor genes. Oncogene 33(17):2157-68.

[289] Chudnovsky Y, Kim D, Zheng S, et al. (2014) ZFHX4 interacts with the NuRD core member CHD4 and regulates the glioblastoma tumor-initiating cell state. Cell Rep 6(2):313-24.

[290] O'Shaughnessy A, Hendrich B (2013) CHD4 in the DNA-damage response and cell cycle progression: not so NuRDy now. Biochem Soc Trans 41(3):777-82.

APPENDIX

REFERENCES

[291] Pan MR, Hsieh HJ, Dai H, et al. (2012) Chromodomain helicase DNA-binding protein 4 (CHD4) regulates homologous recombination DNA repair, and its deficiency sensitizes cells to poly(ADP-ribose) polymerase (PARP) inhibitor treatment. J Biol Chem 287(9):6764-72.

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

[293] Deakyne JS, Mazin AV (2011) Fanconi anemia: at the crossroads of DNA repair. Biochemistry Mosc 76(1):36-48.

[294] Morris LG, Kaufman AM, Gong Y, et al. (2013) Recurrent somatic mutation of FAT1 in multiple human cancers leads to aberrant Wnt activation. Nat Genet 45(3):253-61.

[295] Katoh M (2012) Function and cancer genomics of FAT family genes (review). Int J Oncol 41(6):1913-8.

[296] Jatiani SS, Baker SJ, Silverman LR, et al. (2010) Jak/STAT pathways in cytokine signaling and myeloproliferative disorders: approaches for targeted therapies. Genes Cancer 1(10):979-93.

[297] Levine RL (2012) JAK-mutant myeloproliferative neoplasms. Curr Top Microbiol Immunol 355:119-33.

[298] Pansky A, Hildebrand P, Fasler-Kan E, et al. (2000) Defective Jak-STAT signal transduction pathway in melanoma cells resistant to growth inhibition by interferon-alpha. Int J Cancer 85(5):720-5.

[299] Ren Y, Zhang Y, Liu RZ, et al. (2013) JAK1 truncating mutations in gynecologic cancer define new role of cancer-associated protein tyrosine kinase aberrations. Sci Rep 3:3042.

[300] Xiong H, Zhang ZG, Tian XQ, et al. (2008) Inhibition of JAK1, 2/STAT3 signaling induces apoptosis, cell cycle arrest, and reduces tumor cell invasion in colorectal cancer cells. Neoplasia 10(3):287-97.

[301] Van Schaeybroeck S, Kalimutho M, Dunne PD, et al. (2014) ADAM17-dependent c-MET-STAT3 signaling mediates resistance to MEK inhibitors in KRAS mutant colorectal cancer. Cell Rep 7(6):1940-55.

[302] Moon SU, Kang MH, Sung JH, et al. (2015) Effect of Smad3/4 on chemotherapeutic drug sensitivity in colorectal cancer cells. Oncol Rep 33(1):185-92.

[303] Gordon GM, Lambert QT, Daniel KG, et al. (2010) Transforming JAK1 mutations exhibit differential signalling, FERM domain requirements and growth responses to interferon-γ. Biochem J 432(2):255-65.

[304] Verstovsek S, Mesa RA, Gotlib J, et al. (2013) The clinical benefit of ruxolitinib across patient subgroups: analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. Br J Haematol 161(4):508-16.

[305] Naqvi K, Verstovsek S, Kantarjian H, et al. (2011) A potential role of ruxolitinib in leukemia. Expert Opin Investig Drugs 20(8):1159-66.

[306] Verstovsek S, Kantarjian HM, Estrov Z, et al. (2012) Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. Blood 120(6):1202-9.

[307] Swiatek-Machado K, Mieczkowski J, Ellert-Miklaszewska A, et al. (2012) Novel small molecular inhibitors disrupt the JAK/STAT3 and FAK signaling pathways and exhibit a potent antitumor activity in glioma cells. Cancer Biol Ther 13(8):657-70.

[308] Yan S, Li Z, Thiele CJ (2013) Inhibition of STAT3 with orally active JAK inhibitor, AZD1480, decreases tumor growth in Neuroblastoma and Pediatric Sarcomas In vitro and In vivo. Oncotarget 4(3):433-45.

[309] Wang Y, Trepel JB, Neckers LM, et al. (2010) STA-9090, a small-molecule Hsp90 inhibitor for the potential treatment of cancer. Curr Opin Investig Drugs 11(12):1466-76.

APPENDIX

REFERENCES

[310] van Haaften G, Dalgliesh GL, Davies H, et al. (2009) Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. Nat Genet 41(5):521-3.

[311] Robinson G, Parker M, Kranenburg TA, et al. (2012) Novel mutations target distinct subgroups of medulloblastoma. Nature 488(7409):43-8.

[312] Ho AS, Kannan K, Roy DM, et al. (2013) The mutational landscape of adenoid cystic carcinoma. Nat Genet 45(7):791-8.

[313] Van der Meulen J, Sanghvi V, Mavrakis K, et al. (2015) The H3K27me3 demethylase UTX is a gender-specific tumor suppressor in T-cell acute lymphoblastic leukemia. Blood 125(1):13-21.

[314] Wang L, Chang J, Varghese D, et al. (2013) A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. Nat Commun 4:2035.

[315] Kim JH, Sharma A, Dhar SS, et al. (2014) UTX and MLL4 coordinately regulate transcriptional programs for cell proliferation and invasiveness in breast cancer cells. Cancer Res 74(6):1705-17.

[316] Shen Y, Guo X, Wang Y, et al. (2012) Expression and significance of histone H3K27 demethylases in renal cell carcinoma. BMC Cancer 12:470.

[317] Vicent GP, Nacht AS, Font-Mateu J, et al. (2011) Four enzymes cooperate to displace histone H1 during the first minute of hormonal gene activation. Genes Dev 25(8):845-62.

[318] Hannibal MC, Buckingham KJ, Ng SB, et al. (2011) Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. Am J Med Genet A 155A(7):1511-6.

[319] Morin RD, Mendez-Lago M, Mungall AJ, et al. (2011) Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature 476(7360):298-303.

[320] Cancer Genome Atlas Research Network (2012) Comprehensive genomic characterization of squamous cell lung cancers. Nature 489(7417):519-25.

[321] Wang NJ, Sanborn Z, Arnett KL, et al. (2011) Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc Natl Acad Sci USA 108(43):17761-6.

[322] Klinakis A, Lobry C, Abdel-Wahab O, et al. (2011) A novel tumour-suppressor function for the Notch pathway in myeloid leukaemia. Nature 473(7346):230-3.

[323] Penton AL, Leonard LD, Spinner NB (2012) Notch signaling in human development and disease. Semin Cell Dev Biol 23(4):450-7.

[324] Kopan R, Ilagan MX (2009) The canonical Notch signaling pathway: unfolding the activation mechanism. Cell 137(2):216-33.

[325] Aster JC, Xu L, Karnell FG, et al. (2000) Essential roles for ankyrin repeat and transactivation domains in induction of T-cell leukemia by notch1. Mol Cell Biol 20(20):7505-15.

[326] Weng AP, Ferrando AA, Lee W, et al. (2004) Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 306(5694):269-71.

[327] Huang R, Tang Q, You Q, et al. (2013) Disparity expression of notch1 in benign and malignant colorectal diseases. PLoS ONE 8(12):e81005.

[328] Li Y, Burns JA, Cheney CA, et al. (2010) Distinct expression profiles of Notch-1 protein in human solid tumors: Implications for development of targeted therapeutic monoclonal antibodies. Biologics 4:163-71.

APPENDIX

REFERENCES

[329] Chu D, Zhang Z, Zhou Y, et al. (2011) Notch1 and Notch2 have opposite prognostic effects on patients with colorectal cancer. Ann Oncol 22(11):2440-7.

[330] Debeb BG, Cohen EN, Boley K, et al. (2012) Pre-clinical studies of Notch signaling inhibitor RO4929097 in inflammatory breast cancer cells. Breast Cancer Res Treat 134(2):495-510.

[331] Kamstrup MR, Gjerdrum LM, Biskup E, et al. (2010) Notch1 as a potential therapeutic target in cutaneous T-cell lymphoma. Blood 116(14):2504-12.

[332] Kridel R, Meissner B, Rogic S, et al. (2012) Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. Blood 119(9):1963-71.

[333] Krop I, Demuth T, Guthrie T, et al. (2012) Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J Clin Oncol 30(19):2307-13.

[334] Rosati E, Sabatini R, De Falco F, et al. (2013) γ-Secretase inhibitor I induces apoptosis in chronic lymphocytic leukemia cells by proteasome inhibition, endoplasmic reticulum stress increase and notch down-regulation. Int J Cancer 132(8):1940-53.

[335] Samon JB, Castillo-Martin M, Hadler M, et al. (2012) Preclinical analysis of the γ-secretase inhibitor PF-03084014 in combination with glucocorticoids in T-cell acute lymphoblastic leukemia. Mol Cancer Ther 11(7):1565-75.

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

[337] Pancewicz J, Nicot C (2011) Current views on the role of Notch signaling and the pathogenesis of human leukemia. BMC Cancer 11:502.

[338] Sakata-Yanagimoto M, Chiba S (2012) Notch2 and immune function. Curr Top Microbiol Immunol 360:151-61.

[339] Kiel MJ, Velusamy T, Betz BL, et al. (2012) Whole-genome sequencing identifies recurrent somatic NOTCH2 mutations in splenic marginal zone lymphoma. J Exp Med 209(9):1553-65.

[340] Egloff AM, Grandis JR (2012) Molecular pathways: context-dependent approaches to Notch targeting as cancer therapy. Clin Cancer Res 18(19):5188-95.

[341] Beà S, Valdés-Mas R, Navarro A, et al. (2013) Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. Proc Natl Acad Sci USA 110(45):18250-5.

[342] McDaniell R, Warthen DM, Sanchez-Lara PA, et al. (2006) NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. Am J Hum Genet 79(1):169-73.

[343] Yen WC, Fischer MM, Axelrod F, et al. (2015) Targeting notch signaling with a notch2/notch3 antagonist (tarextumab) inhibits tumor growth and decreases tumor-initiating cell frequency. Clin Cancer Res 21(9):2084-95.

[344] Espinoza I, Miele L (2013) Notch inhibitors for cancer treatment. Pharmacol Ther 139(2):95-110.

[345] Lamarche BJ, Orazio NI, Weitzman MD (2010) The MRN complex in double-strand break repair and telomere maintenance. FEBS Lett 584(17):3682-95.

[346] Hohl M, Kwon Y, Galván SM, et al. (2011) The Rad50 coiled-coil domain is indispensable for Mre11 complex functions. Nat Struct Mol Biol 18(10):1124-31.

[347] Tommiska J, Seal S, Renwick A, et al. (2006) Evaluation of RAD50 in familial breast cancer predisposition. Int J Cancer 118(11):2911-6.

APPENDIX

REFERENCES

[348] Kuusisto KM, Bebel A, Vihinen M, et al. (2011) Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. Breast Cancer Res 13(1):R20.

[349] Gao J, Zhang H, Arbman G, et al. (2008) RAD50/MRE11/NBS1 proteins in relation to tumour development and prognosis in patients with microsatellite stable colorectal cancer. Histol Histopathol 23(12):1495-502.

[350] Vilar E, Bartnik CM, Stenzel SL, et al. (2011) MRE11 deficiency increases sensitivity to poly(ADP-ribose) polymerase inhibition in microsatellite unstable colorectal cancers. Cancer Res 71(7):2632-42.

[351] Weigman VJ, Chao HH, Shabalin AA, et al. (2012) Basal-like Breast cancer DNA copy number losses identify genes involved in genomic instability, response to therapy, and patient survival. Breast Cancer Res Treat 133(3):865-80.

[352] Oplustilova L, Wolanin K, Mistrik M, et al. (2012) Evaluation of candidate biomarkers to predict cancer cell sensitivity or resistance to PARP-1 inhibitor treatment. Cell Cycle 11(20):3837-50.

[353] Tahara M, Inoue T, Sato F, et al. (2014) The use of Olaparib (AZD2281) potentiates SN-38 cytotoxicity in colon cancer cells by indirect inhibition of Rad51-mediated repair of DNA double-strand breaks. Mol Cancer Ther 13(5):1170-80.

[354] Koppensteiner R, Samartzis EP, Noske A, et al. (2014) Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer in vitro. PLoS ONE 9(6):e100041.

[355] Vilar E, Scaltriti M, Balmaña J, et al. (2008) Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer 99(10):1607-12.

[356] Abuzeid WM, Jiang X, Shi G, et al. (2009) Molecular disruption of RAD50 sensitizes human tumor cells to cisplatin-based chemotherapy. J Clin Invest 119(7):1974-85.

[357] Figures MR, Wobb J, Araki K, et al. (2009) Head and neck squamous cell carcinoma targeted chemosensitization. Otolaryngol Head Neck Surg 141(2):177-83.

[358] Al-Ahmadie H, Iyer G, Hohl M, et al. (2014) Synthetic Lethality in ATM-Deficient RAD50-Mutant Tumors Underlies Outlier Response to Cancer Therapy. Cancer Discov 4(9):1014-21.

[359] Burkhart DL, Sage J (2008) Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer 8(9):671-82.

[360] Knudsen ES, Knudsen KE (2008) Tailoring to RB: tumour suppressor status and therapeutic response. Nat Rev Cancer 8(9):714-24.

[361] Berge EO, Knappskog S, Geisler S, et al. (2010) Identification and characterization of retinoblastoma gene mutations disturbing apoptosis in human breast cancers. Mol Cancer 9:173.

[362] Giacinti C, Giordano A (2006) RB and cell cycle progression. Oncogene 25(38):5220-7.

[363] Otterson GA, Chen Wd, Coxon AB, et al. (1997) Incomplete penetrance of familial retinoblastoma linked to germ-line mutations that result in partial loss of RB function. Proc Natl Acad Sci USA 94(22):12036-40.

[364] Otterson GA, Modi S, Nguyen K, et al. (1999) Temperature-sensitive RB mutations linked to incomplete penetrance of familial retinoblastoma in 12 families. Am J Hum Genet 65(4):1040-6.

[365] Qin XQ, Chittenden T, Livingston DM, et al. (1992) Identification of a growth suppression domain within the retinoblastoma gene product. Genes Dev 6(6):953-64.

[366] Rubin SM, Gall AL, Zheng N, et al. (2005) Structure of the Rb C-terminal domain bound to E2F1-DP1: a mechanism for phosphorylation-induced E2F release. Cell 123(6):1093-106.

APPENDIX

REFERENCES

[367] Sun H, Chang Y, Schweers B, et al. (2006) An E2F binding-deficient Rb1 protein partially rescues developmental defects associated with Rb1 nullizygosity. Mol Cell Biol 26(4):1527-37.

[368] Chen Z, Moran K, Richards-Yutz J, et al. (2014) Enhanced sensitivity for detection of low-level germline mosaic RB1 mutations in sporadic retinoblastoma cases using deep semiconductor sequencing. Hum Mutat 35(3):384-91.

[369] Yun J, Li Y, Xu CT, et al. (2011) Epidemiology and Rb1 gene of retinoblastoma. Int J Ophthalmol 4(1):103-9.

[370] Houston SK, Murray TG, Wolfe SQ, et al. (2011) Current update on retinoblastoma. Int Ophthalmol Clin 51(1):77-91.

[371] Ng AK, Kenney LB, Gilbert ES, et al. (2010) Secondary malignancies across the age spectrum. Semin Radiat Oncol 20(1):67-78.

[372] Collard TJ, Urban BC, Patsos HA, et al. (2012) The retinoblastoma protein (Rb) as an anti-apoptotic factor: expression of Rb is required for the anti-apoptotic function of BAG-1 protein in colorectal tumour cells. Cell Death Dis 3:e408.

[373] Lai PS, Cheah PY, Kadam P, et al. (2006) Overexpression of RB1 transcript is significantly correlated with 13q14 allelic imbalance in colorectal carcinomas. Int J Cancer 119(5):1061-6.

[374] Catela Ivkovic T, Aralica G, Cacev T, et al. (2013) miR-106a overexpression and pRB downregulation in sporadic colorectal cancer. Exp Mol Pathol 94(1):148-54.

[375] Poller DN, Baxter KJ, Shepherd NA (1997) p53 and Rb1 protein expression: are they prognostically useful in colorectal cancer? Br J Cancer 75(1):87-93.

[376] Hook KE, Garza SJ, Lira ME, et al. (2012) An integrated genomic approach to identify predictive biomarkers of response to the aurora kinase inhibitor PF-03814735. Mol Cancer Ther 11(3):710-9.

[377] Allaman-Pillet N, Oberson A, Munier F, et al. The Bcl-2/Bcl-XL inhibitor ABT-737 promotes death of retinoblastoma cancer cells. Ophthalmic Genet 34(1-2):1-13.

[378] Viatour P, Ehmer U, Saddic LA, et al. (2011) Notch signaling inhibits hepatocellular carcinoma following inactivation of the RB pathway. J Exp Med 208(10):1963-76.

[379] Derenzini M, Donati G, Mazzini G, et al. (2008) Loss of retinoblastoma tumor suppressor protein makes human breast cancer cells more sensitive to antimetabolite exposure. Clin Cancer Res 14(7):2199-209.

[380] Fry DW, Harvey PJ, Keller PR, et al. (2004) Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther 3(11):1427-38.

[381] Dean JL, Thangavel C, McClendon AK, et al. (2010) Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. Oncogene 29(28):4018-32.

[382] Dean JL, McClendon AK, Hickey TE, et al. (2012) Therapeutic response to CDK4/6 inhibition in breast cancer defined by ex vivo analyses of human tumors. Cell Cycle 11(14):2756-61.

[383] Garnett MJ, Edelman EJ, Heidorn SJ, et al. (2012) Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 483(7391):570-5.

[384] Rio-Machín A, Menezes J, Maiques-Diaz A, et al. (2012) Abrogation of RUNX1 gene expression in de novo myelodysplastic syndrome with t(4;21)(q21;q22). Haematologica 97(4):534-7.

[385] Silva FP, Morolli B, Storlazzi CT, et al. (2003) Identification of RUNX1/AML1 as a classical tumor suppressor gene. Oncogene 22(4):538-47.

APPENDIX

REFERENCES

[386] Scheitz CJ, Tumbar T (2013) New insights into the role of Runx1 in epithelial stem cell biology and pathology. J Cell Biochem 114(5):985-93.

[387] Zhao LJ, Wang YY, Li G, et al. (2012) Functional features of RUNX1 mutants in acute transformation of chronic myeloid leukemia and their contribution to inducing murine full-blown leukemia. Blood 119(12):2873-82.

[388] Yamamoto K, Tsuzuki S, Minami Y, et al. (2013) Functionally deregulated AML1/RUNX1 cooperates with BCR-ABL to induce a blastic phase-like phenotype of chronic myelogenous leukemia in mice. PLoS ONE 8(9):e74864.

[389] Cammenga J, Niebuhr B, Horn S, et al. (2007) RUNX1 DNA-binding mutants, associated with minimally differentiated acute myelogenous leukemia, disrupt myeloid differentiation. Cancer Res 67(2):537-45.

[390] Matheny CJ, Speck ME, Cushing PR, et al. (2007) Disease mutations in RUNX1 and RUNX2 create nonfunctional, dominant-negative, or hypomorphic alleles. EMBO J 26(4):1163-75.

[391] Michaud J, Wu F, Osato M, et al. (2002) In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. Blood 99(4):1364-72.

[392] Li Z, Yan J, Matheny CJ, et al. (2003) Energetic contribution of residues in the Runx1 Runt domain to DNA binding. J Biol Chem 278(35):33088-96.

[393] Slattery ML, Lundgreen A, Herrick JS, et al. (2011) Associations between genetic variation in RUNX1, RUNX2, RUNX3, MAPK1 and eIF4E and riskof colon and rectal cancer: additional support for a TGF-β-signaling pathway. Carcinogenesis 32(3):318-26.

[394] Fijneman RJ, Anderson RA, Richards E, et al. (2012) Runx1 is a tumor suppressor gene in the mouse gastrointestinal tract. Cancer Sci 103(3):593-9.

[395] Inoue A, Kawakami C, Takitani K, et al. (2014) Azacitidine in the treatment of pediatric therapy-related myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation. J Pediatr Hematol Oncol 36(5):e322-4.

[396] Buchi F, Masala E, Rossi A, et al. (2014) Redistribution of H3K27me3 and acetylated histone H4 upon exposure to azacitidine and decitabine results in de-repression of the AML1/ETO target gene IL3. Epigenetics 9(3):387-95.

[397] Braun T, Itzykson R, Renneville A, et al. (2011) Molecular predictors of response to decitabine in advanced chronic myelomonocytic leukemia: a phase 2 trial. Blood 118(14):3824-31.

[398] Tobiasson M, McLornan DP, Karimi M, et al. (2016) Mutations in histone modulators are associated with prolonged survival during azacitidine therapy. Oncotarget ePub Mar 2016.

[399] Odenike OM, Alkan S, Sher D, et al. (2008) Histone deacetylase inhibitor romidepsin has differential activity in core binding factor acute myeloid leukemia. Clin Cancer Res 14(21):7095-101.

[400] Barbetti V, Gozzini A, Rovida E, et al. (2008) Selective anti-leukaemic activity of low-dose histone deacetylase inhibitor ITF2357 on AML1/ETO-positive cells. Oncogene 27(12):1767-78.

[401] Hu Z, Gu X, Baraoidan K, et al. (2011) RUNX1 regulates corepressor interactions of PU.1. Blood 117(24):6498-508.

[402] Bots M, Verbrugge I, Martin BP, et al. (2014) Differentiation therapy for the treatment of t(8;21) acute myeloid leukemia using histone deacetylase inhibitors. Blood 123(9):1341-52.

[403] Sun XJ, Wei J, Wu XY, et al. (2005) Identification and characterization of a novel human histone H3 lysine 36-specific methyltransferase. J Biol Chem 280(42):35261-71.

APPENDIX

REFERENCES

[404] Faber PW, Barnes GT, Srinidhi J, et al. (1998) Huntingtin interacts with a family of WW domain proteins. Hum Mol Genet 7(9):1463-74.

[405] Al Sarakbi W, Sasi W, Jiang WG, et al. (2009) The mRNA expression of SETD2 in human breast cancer: correlation with clinico-pathological parameters. BMC Cancer 9:290.

[406] Varela I, Tarpey P, Raine K, et al. (2011) Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. Nature 469(7331):539-42.

[407] Mar BG, Bullinger LB, McLean KM, et al. (2014) Mutations in epigenetic regulators including SETD2 are gained during relapse in paediatric acute lymphoblastic leukaemia. Nat Commun 5:3469.

[408] Wang Q, Cheng T (2014) Evidences for mutations in the histone modifying gene SETD2 as critical drivers in leukemia development. Sci China Life Sci 57(9):944-6.

[409] Zhu X, He F, Zeng H, et al. (2014) Identification of functional cooperative mutations of SETD2 in human acute leukemia. Nat Genet 46(3):287-93.

[410] Wilson BG, Roberts CW (2011) SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer 11(7):481-92.

[411] Trotter KW, Fan HY, Ivey ML, et al. (2008) The HSA domain of BRG1 mediates critical interactions required for glucocorticoid receptor-dependent transcriptional activation in vivo. Mol Cell Biol 28(4):1413-26.

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

[413] Dykhuizen EC, Hargreaves DC, Miller EL, et al. (2013) BAF complexes facilitate decatenation of DNA by topoisomerase IIα. Nature 497(7451):624-7.

[414] Watanabe T, Semba S, Yokozaki H (2011) Regulation of PTEN expression by the SWI/SNF chromatin-remodelling protein BRG1 in human colorectal carcinoma cells. Br J Cancer 104(1):146-54.

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

[416] Bai J, Mei P, Zhang C, et al. (2013) BRG1 is a prognostic marker and potential therapeutic target in human breast cancer. PLoS ONE 8(3):e59772.

[417] Kim KH, Kim W, Howard TP, et al. (2015) SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. Nat Med 21(12):1491-6.

[418] Jelinic P, Schlappe BA, Conlon N, et al. (2016) Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type. Mod Pathol 29(1):60-6.

[419] Karnezis AN, Wang Y, Ramos P, et al. (2015) Dual loss of the SWI/SNF complex ATPases SMARCA4/BRG1 and SMARCA2/BRM is highly sensitive and specific for small cell carcinoma of the ovary, hypercalcemic type. J Pathol ePub Sep 2015.

[420] Kothandapani A, Gopalakrishnan K, Kahali B, et al. (2012) Downregulation of SWI/SNF chromatin remodeling factor subunits modulates cisplatin cytotoxicity. Exp Cell Res 318(16):1973-86.

[421] Otte A, Rauprich F, Hillemanns P, et al. (2014) In vitro and in vivo therapeutic approach for a small cell carcinoma of the ovary hypercalcaemic type using a SCCOHT-1 cellular model. Orphanet J Rare Dis 9:126.

APPENDIX

REFERENCES

[422] Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. (2014) Olaparib Monotherapy in Patients With Advanced Cancer and a Germline BRCA1/2 Mutation. J Clin Oncol ePub Nov 2014.

[423] Leichman L, Groshen S, O'Neil BH, et al. (2016) Phase II Study of Olaparib (AZD-2281) After Standard Systemic Therapies for Disseminated Colorectal Cancer. Oncologist ePub Jan 2016.

[424] Ribas A, Gonzalez R, Pavlick A, et al. (2014) Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 15(9):954-65.

[425] Abdel-Wahab O, Klimek VM, Gaskell AA, et al. (2014) Efficacy of intermittent combined RAF and MEK inhibition in a patient with concurrent BRAF- and NRAS-mutant malignancies. Cancer Discov 4(5):538-45.

[426] Yamaguchi T, Kakefuda R, Tajima N, et al. (2011) Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo. Int J Oncol 39(1):23-31.

[427] Watanabe M, Sowa Y, Yogosawa M, et al. (2013) Novel MEK inhibitor trametinib and other retinoblastoma gene (RB)-reactivating agents enhance efficacy of 5-fluorouracil on human colon cancer cells. Cancer Sci 104(6):687-93.

[428] Gilmartin AG, Bleam MR, Groy A, et al. (2011) GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. Clin Cancer Res 17(5):989-1000.

[429] Infante JR, Papadopoulos KP, Bendell JC, et al. (2013) A phase 1b study of trametinib, an oral Mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. Eur J Cancer 49(9):2077-85.

[430] Infante JR, Fecher LA, Falchook GS, et al. (2012) Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 13(8):773-81.

[431] Leijen S, Middleton MR, Tresca P, et al. (2012) Phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor RO4987655 (CH4987655) in patients with advanced solid tumors. Clin Cancer Res 18(17):4794-805.

[432] Zimmer L, Barlesi F, Martinez-Garcia M, et al. (2014) Phase I Expansion and Pharmacodynamic Study of the Oral MEK Inhibitor RO4987655 (CH4987655) in Selected Patients with Advanced Cancer with RAS-RAF Mutations. Clin Cancer Res 20(16):4251-61.

[433] Tolcher AW, Bendell JC, Papadopoulos KP, et al. (2014) A Phase IB Trial of the Oral MEK Inhibitor Trametinib (GSK1120212) in Combination With Everolimus in Patients With Advanced Solid Tumors. Ann Oncol ePub Oct 2014.

[434] Bennouna J, Lang I, Valladares-Ayerbes M, et al. (2011) A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. Invest New Drugs 29(5):1021-8.

[435] Weekes CD, Von Hoff DD, Adjei AA, et al. (2013) Multicenter phase I trial of the mitogen-activated protein kinase 1/2 inhibitor BAY 86-9766 in patients with advanced cancer. Clin Cancer Res 19(5):1232-43.

[436] Robert C, Long GV, Brady B, et al. (2014) Nivolumab in Previously Untreated Melanoma without BRAF Mutation. N Engl J Med ePub Nov 2014.

[437] Weber JS, D'Angelo SP, Minor D, et al. (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 16(4):375-84.

[438] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. (2015) Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 373(1):23-34.

APPENDIX

REFERENCES

[439] Postow MA, Chesney J, Pavlick AC, et al. (2015) Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 372(21):2006-17.

[440] Topalian SL, Sznol M, McDermott DF, et al. (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 32(10):1020-30.

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

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

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

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

[445] Hamanishi J, Mandai M, Ikeda T, et al. (2015) Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol 33(34):4015-22.

[446] Ansell SM, Lesokhin AM, Borrello I, et al. (2014) PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. N Engl J Med ePub Dec 2014.

APPENDIX

ABOUT FOUNDATIONONE™

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

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test 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 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 for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne 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 analytical methodology has identified as being present in <10% of the assayed tumor DNA.

The Report incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research.

NOTE: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

Treatment Decisions are Responsibility of Physician: Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report.

Certain sample or variant characteristics may result in reduced sensitivity. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

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

For more comprehensive information please log on to the Interactive Cancer Explorer™
To set up your Interactive Cancer Explorer account, contact your sales representative or call (888) 988-3639.