QIAGEN Genomic Services	
Report Date	Nov 20, 2020
Age	67
Gender	Female

Genomic Profiling Service

The QIAGEN Genomics Profiling Service is intended exclusively for research use only (RUO). This service is not intended for the diagnosis, prevention or treatment of a disease.

Specimen information	
Accession Number	DNA10_TSO500
Diagnosis	Colorectal Adenocarcinoma
Collection site	Colon / rectum
Type	Biopsy
Collection date	Nov 20, 2020

QIAseq Pan-Cancer Multimodal Panel Analysis: Somatic Cancer

Simultaneous and comprehensive genomic profiling of DNA variants, RNA fusions and assessing TMB/MSI in solid tumors and heme malignancies.

Overall comment

Any report comments

Analysis results: Positive

2 Biomarkers	Approved treatments	Other findings
Tumor Mutation Burden: TMB-high (56.3 Mutations/Megabase)	Pembrolizumab	Trials: 2 Phase 2 2 Phase 1
Microsatellite Status: MSI-high	Ipilimumab/nivolumab Pembrolizumab	Other Indications: nivolumab Trials: 1 Phase 3 8 Phase 2 1 Early Phase 1
1 Variant of strong clinical significance, Tier 1	**Approved treatments**	**Other findings**
KRAS: p.G12D, Pathogenic	-	**Resistance: cetuximab, panitumumab** Trials: 2 Phase 2 3 Phase 1/Phase 2 4 Phase 1
6 Variants of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
FGFR3: amplification, Pathogenic	-	Trials: 6 Phase 2 3 Phase 1/Phase 2 1 Phase 1
KIT: amplification, Pathogenic	-	**Resistance: crizotinib, imatinib** Trials: 3 Phase 2 1 Phase 1/Phase 2 5 Phase 1
NOTCH1: p.F357del, Likely Pathogenic	-	-

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Interactions

None

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 3.

Report content

6 Variants of potential clinical significance, Tier 2	Approved treatments	Other findings
PDGFRA: amplification, Pathogenic	-	**Resistance: imatinib** Trials: 3 Phase 2 1 Phase 1/Phase 2 4 Phase 1
PIK3CA: amplification, Pathogenic	-	Trials: 2 Phase 1/Phase 2 4 Phase 1
TP53: p.P278S, Pathogenic	-	Other Indications: bortezomib /rituximab, lenalidomide/rituximab, rituximab **Resistance: lorlatinib** Trials: 3 Phase 1

2 Variants of biological significance, Tier 3	9 Variants of uncertain significance, Tier 3

MPL †: p.R102P, Likely Pathogenic

SHQ1 †: p.D277fs*27, Pathogenic

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

GUIDELINES

For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, the NCCN guidelines (v.4.2020) recommend against the use of cetuximab and panitumumab. The NCCN Guidelines (v. 4.2020) suggest testing for microsatellite instability (MSI) in all newly diagnosed patients with colon cancer; nivolumab, alone or in combination with ipilimumab, and pembrolizumab are listed as possible treatment options for MSI-high colorectal carcinoma patients, depending on the physician's evaluation of the individual patient. The NCCN Guidelines (v.4.2020) additionally note that stage 2 MSI-high colorectal carcinoma patients may not benefit from adjuvant 5FU therapy.

TREATMENT OPTIONS

Therapies with potential clinical benefit (6)

PEMBROLIZUMAB

Pembrolizumab, a programmed death receptor-1 (PD-1)-blocking antibody, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma; for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection; in combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations; in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, for the first-line treatment of patients with metastatic squamous NSCLC; as a single agent for treating patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab); for treating patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test; and, in combination with axitinib, for the first-line treatment of patients with advanced renal cell carcinoma; pembrolizumab is also FDA-approved as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic; for treating patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy; in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell cancer (HNSCC); as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test; as a single agent for treating patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy; for treating adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL); for treating pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy; for treating adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy; for treating patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status; for treating patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; for treating patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy; for treating adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC); for treating patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine-and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy; for treating patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy; for treating patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test; for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib; for treating adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma; in combination with lenvatinib, for treating patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation; as a single agent for treating adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options; for treating patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation; and in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic Triple-Negative Breast Cancer (TNBC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test; pembrolizumab is also EMA-approved for treating adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV; locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy; as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 with a CPS ≥ 1; for treating adult patients with recurrent or metastatic HNSCC whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy; and as a single agent for the first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

Sensitive
Biomarkers: Tumor Mutation Burden: TMB-high, Tier 1A
Microsatellite Status: MSI-high, Tier 1A

Therapies with potential clinical benefit (6)

IPILIMUMAB/NIVOLUMAB

Nivolumab, a PD-1 blocking antibody, in combination with ipilimumab, a CTLA-4 blocking antibody, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma; and intermediate or poor risk, previously untreated advanced renal cell carcinoma; nivolumab, in combination with ipilimumab, is FDA-approved for treating adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib; as first-line treatment for adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; in combination with 2 cycles of platinum-doublet chemotherapy, as first-line treatment for adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations; and as first-line treatment for adult patients with unresectable malignant pleural mesothelioma.

Sensitive
Biomarker: Microsatellite Status: MSI-high, Tier 1A

NIVOLUMAB

Nivolumab, a PD-1 blocking antibody, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab; melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting; metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab); advanced renal cell carcinoma who have received prior anti-angiogenic therapy; intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab; for treating adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT; for treating patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy; and locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; nivolumab is also FDA-approved for treating adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab; metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy; for treating patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy; for treating adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab; for treating adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab; for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab; and for treating patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.

Sensitive
Biomarker: Microsatellite Status: MSI-high, Tier 1A

BORTEZOMIB/RITUXIMAB

Bortezomib, a proteasome inhibitor, in combination with rituximab, a CD20-directed cytolytic antibody, and cyclophosphamide, an alkylating drug, and doxorubicin, an anthracycline topoisomerase inhibitor, and prednisone, a corticosteroid, is EMA-approved for treating adult patients with previously untreated mantle cell lymphoma, who are unsuitable for haematopoietic stem cell transplantation.

Sensitive

Gene	Classification	Variant
TP53	Tier 2C Pathogenic	p.P278S c.832C>T

LENALIDOMIDE/RITUXIMAB

Lenalidomide, a thalidomide analogue, in combination with rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating patients with previously treated follicular lymphoma (FL); lenalidomide, in combination with rituximab, is FDA-approved for treating patients with previously treated marginal zone lymphoma (MZL).

Sensitive

Gene	Classification	Variant
TP53	Tier 2C Pathogenic	p.P278S c.832C>T

RITUXIMAB

Rituximab, a CD20-directed cytolytic antibody, is FDA-approved for treating adult patients with relapsed or refractory, low grade or follicular, CD20-positive B cell Non-Hodgkin's Lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens; previously untreated and

Therapies with potential clinical benefit (6)

previously treated CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rituximab is EMA-approved for treating adult patients with previously untreated stage III-IV follicular lymphoma in combination with chemotherapy; follicular lymphoma (maintenance therapy) responding to induction therapy; stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy; CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy; for treating paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL), in combination with chemotherapy; and for treating patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy.

Sensitive

Gene	Classification	Variant
TP53	Tier 2C Pathogenic	p.P278S c.832C>T

Therapies associated with resistance (5)

CETUXIMAB

Cetuximab, an epidermal growth factor receptor antagonist, is FDA-approved for treating patients with locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU; recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy; KRAS wild-type, EGFR-expressing, metastatic colorectal cancer in combination with FOLFIRI for first-line treatment, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan; cetuximab is EMA-approved for treating patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan; squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

PANITUMUMAB

Panitumumab, an epidermal growth factor receptor (EGFR) antagonist, is FDA- and EMA-approved for treating patients with wild-type RAS (defined as wild-type in both KRAS and NRAS) metastatic colorectal cancer in combination with FOLFOX for first-line treatment, as monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy; and panitumumab is EMA-approved for treating patients with wild-type RAS metastatic colorectal cancer in first-line in combination with FOLFIRI, and in second-line in combination with FOLFIRI for those who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

CRIZOTINIB

Crizotinib, a kinase inhibitor, is FDA- and EMA-approved for treating patients with metastatic non-small cell lung cancer whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive.

Resistance

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification

IMATINIB

Imatinib, a protein tyrosine kinase inhibitor, is FDA- and EMA-approved for treating adult and pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia in chronic phase; for treating patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; for treating adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia; for treating pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia in combination with chemotherapy; for treating adult patients with myelodysplastic /myeloproliferative diseases associated with PDGFR gene re-arrangements as determined with an FDA-approved test; unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans; Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors; and for adjuvant treatment of adult patients following resection of Kit (CD117) positive gastrointestinal stromal tumors; imatinib is FDA-approved for treating adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test, or with c-Kit mutational status unknown; and hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase or who are FIP1L1-PDGFRα fusion kinase negative or unknown; imatinib is EMA-approved for treating adult patients with newly diagnosed Philadelphia

Therapies associated with resistance (5)

chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in combination with chemotherapy; and advanced hypereosinophilic syndrome and/or chronic eosinophilic leukemia with FIP1L1-PDGFRα rearrangement.

Resistance

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

LORLATINIB

Lorlatinib, a kinase inhibitor, is FDA-approved for treating patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.

Resistance

Gene	Classification	Variant
TP53	Tier 2C Pathogenic	p.P278S c.832C>T

AVAILABLE CLINICAL TRIALS

Phase 3 clinical trials (1)

OXALIPLATIN, IRINOTECAN, CETUXIMAB, IPILIMUMAB, LEUCOVORIN, BEVACIZUMAB, 5-FLUOROURACIL, NIVOLUMAB

A Phase 3 Randomized Clinical Trial of Nivolumab Alone, Nivolumab in Combination With Ipilimumab, or an Investigator's Choice Chemotherapy in Participants With Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
NCT04008030

Qualifying variant

Biomarker	Classification	Score
MSI-high	Tier 1A Pathogenic	-

Contact
United States: CA, CO, IL, NY, OR, PA, TX, VA
Recruiting sites have contact information. Please contact the sites directly. If there is no contact information; Clinical.Trials@bms.com;

Phase 2 clinical trials (16)

IPILIMUMAB, NIVOLUMAB

A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination With Ipilimumab or Nivolumab Monotherapy in Participants With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)
NCT03668119

Qualifying variant

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	56.3 Mutations/Megabase

Contact
United States: CA, CO, MN, NC, NY, OR, TX
Recruiting sites have contact information. Please contact the sites directly. If there is no contact information; Clinical.Trials@bms.com;

PEMBROLIZUMAB, IPILIMUMAB, NIVOLUMAB

Targeted Agent and Profiling Utilization Registry (TAPUR) Study
NCT02693535

Qualifying variants

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	56.3 Mutations/Megabase
MSI-high	Tier 1A Pathogenic	-

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

Contact
United States: AL, AZ, CA, FL, GA, HI, IL, IN, ME, MI, NC, ND, NE, NH, OK, OR, PA, SD, TX, UT, VA, WA
Pam Mangat, MS; pam.mangat@asco.org;

CYCLOPHOSPHAMIDE, FLUDARABINE PHOSPHATE

A Phase 2 Study to Evaluate the Efficacy and Safety of Adoptive Transfer of Autologous Tumor Infiltrating Lymphocytes in Patients With Advanced Solid Cancers
NCT03935893

Qualifying variant

Contact

Phase 2 clinical trials (16)

Biomarker	Classification	Score	
MSI-high	Tier 1A Pathogenic	-	United States: PA Samantha Devine, PA-C; perkinssj@upmc.edu; 412-623-5960;

CELECOXIB, RINTATOLIMOD, IFNA2

Phase 2a Study Evaluating a Chemokine-Modulatory Regimen in Patients With Colorectal Cancer Metastatic to the Liver
NCT03403634

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: NY Sarbajit Mukherjee, MD;

PEMBROLIZUMAB, CYCLOPHOSPHAMIDE, DPX-SURVIVAC

A Phase 2, Open-label, Multicenter, Study of an Immunotherapeutic Treatment, DPX-Survivac in Combination With Low Dose Cyclophosphamide and Pembrolizumab, in Subjects With Selected Advanced and Recurrent Solid Tumours.
NCT03836352

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: CA, FL, GA, KY, LA, NY, TX

BMS-986016, NIVOLUMAB

Phase 2 Study of Nivolumab and Relatlimab in Advanced Mismatch Repair Deficient Cancers Resistant to Prior PD-(L)1 Inhibitor
NCT03607890

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: MD Susan Sartorius-Mergenthaler, RN; Sartosu@jhmi.edu; 410-614-3644;

PEMBROLIZUMAB, ALT-803, NIVOLUMAB

QUILT-3.055: A Phase IIb, Multicohort, Open-Label Study of Combination Immunotherapies in Patients Who Have Previously Received Treatment With PD-1/PD-L1 Immune Checkpoint Inhibitors
NCT03228667

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: AR, CA, FL, IA, IN, KY, MA, MI, MN, MO, MT, NH, NY, OH, OR, SC, SD, TN, TX, VA Jayson Garmizo, MEng; Jayson.Garmizo@ImmunityBio.com; 310-912-2230;

IPILIMUMAB, NIVOLUMAB

Nivolumab and Ipilimumab and Radiation Therapy in Microsatellite Stable (MSS) and Microsatellite Instability (MSI) High Colorectal and Pancreatic Cancer
NCT03104439

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: MA Theodore Hong; tshong1@partners.org; 617-724-8770;

PEMBROLIZUMAB

A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)
NCT02628067

Qualifying variant

Biomarker	Classification	Score	Contact
MSI-high	Tier 1A Pathogenic	-	United States: CA, CO, FL, MA, MD, NJ, TX Toll Free Number; 1-888-577-8839;

TRAMETINIB, PANITUMUMAB

A Phase II Enrichment Study of Panitumumab as a Single Agent or in Combination With Trametinib in Anti-EGFR-Refractory Stage IV Colorectal Cancer Patients
NCT03087071

Phase 2 clinical trials (16)

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

Contact
United States: TX
Christine Parseghian; cparseghian@mdanderson.org;
(713) 795-9280;

BINIMETINIB, TRIFLURIDINE, TIPIRACIL, PALBOCICLIB

Combination of MEK Inhibitor Binimetinib and CDK4/6 Inhibitor Palbociclib in KRAS and NRAS Mutant Metastatic Colorectal Cancers
NCT03981614

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

Contact
United States: AZ, KS, NC, TN, TX
Scott Kopetz;

TRIFLURIDINE, REGORAFENIB, TIPIRACIL

A Randomized Study Evaluating Tailoring of Advanced/Metastatic Colorectal Cancer (CRC) Therapy Using Circulating Cell-Free Tumor DNA (ctDNA) (TACT-D)
NCT03844620

Qualifying variants

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

Contact
United States: TX
Kanwal Raghav; kpraghav@mdanderson.org;
713-792-2828;

RUXOLITINIB, REGORAFENIB, CAPECITABINE

An Open-Label, Multicenter, Rollover Study to Enable Continued Treatment Access for Subjects Previously Enrolled in Studies of Ruxolitinib
NCT02955940

Qualifying variants

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

Contact
United States: KY, NY, TX
Fitzroy Dawkins, MD;

INFIGRATINIB

A Phase II Study of Oral Infigratinib in Adult Patients With Advanced or Metastatic Solid Tumors With FGFR1-3 Gene Fusions or Other FGFR Genetic Alterations
NCT04233567

Qualifying variant

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification

Contact
United States: OH
The Ohio State University Comprehensive Cancer Center;
OSUCCCClinicaltrials@osumc.edu;
1-800-293-5066;

ERDAFITINIB

Molecular Analysis for Therapy Choice (MATCH)
NCT02465060

Qualifying variant

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification

Contact
United States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NE, NH, NJ, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY
Keith T Flaherty;

PONATINIB

Phase II Study of Ponatinib for Advanced Cancers With Genomic Alterations in Fibroblastic Growth Factor Receptor (FGFR) and Other Genomic Targets (KIT, PDGFRá, RET FLT3, ABL1)
NCT02272998

Qualifying variant

Contact
United States: OH

Phase 2 clinical trials (16)

Gene	Classification	Variant	
FGFR3	Tier 2C Pathogenic	amplification	The Ohio State University Comprehensive Cancer Center; Jamesline@osumc.edu; 1-800-293-5066;

Phase 1/Phase 2 clinical trials (8)

ZOTATIFIN

A Phase 1-2 Dose-Escalation and Cohort-Expansion Study of Intravenous Zotatifin (eFT226) in Subjects With Selected Advanced Solid Tumor Malignancies
NCT04092673

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A	United States: MI, OH, TX Robert Sikorski; clinicaltrials@effector.com; 1-858-925-8215;

NAVITOCLAX, TRAMETINIB

An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS or NRAS Mutation-Positive Advanced Solid Tumors
NCT02079740

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A	United States: MA Ryan B Corcoran;

CYCLOPHOSPHAMIDE, ANTI-KRAS G12D MTCR, ALDESLEUKIN, FLUDARABINE PHOSPHATE

A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients
NCT03745326

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A	United States: MD NCI SB Immunotherapy Recruitment Center; irc@nih.gov; (866) 820-4505;

PEMBROLIZUMAB, REGORAFENIB

A Phase I/II Study of Regorafenib and Pembrolizumab in Metastatic Colorectal Cancer Patients in 3rd and 4th Line Setting
NCT03657641

Qualifying variants

Gene	Classification	Variant	Contact
FGFR3	Tier 2C Pathogenic	amplification	United States: CA Xiomara Menendez, RN; Xiomara.Menendez@med.usc.edu; 323-409-4368;
KIT	Tier 2C Pathogenic	amplification	
PDGFRA	Tier 2C Pathogenic	amplification	

SELPERCATINIB

A Phase 1/2 Study of Oral LOXO-292 in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001)
NCT03157128

Qualifying variant

Gene	Classification	Variant	Contact
FGFR3	Tier 2C Pathogenic	amplification	United States: AZ, CA, CO, CT, FL, GA, IL, LA, MA, MD, MI, MN, MO, NC, NV, NY, OH, OR, PA, TN, TX, UT, VA, WI Patient Advocacy; clinicaltrials@loxooncology.com; 855-738-4292;

PEMBROLIZUMAB, DOCETAXEL, TRASTUZUMAB, GEMCITABINE, CISPLATIN, PEMIGATINIB

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054828 in Subjects With Advanced Malignancies (FIGHT-101)
NCT02393248

Qualifying variant

Contact
United States: AL, FL, GA, MO, NC, NJ, NY, OH, TX

Phase 1/Phase 2 clinical trials (8)

Gene	Classification	Variant	Incyte Call Center;
FGFR3	Tier 2C Pathogenic	amplification	1-855-463-3463;

COPANLISIB, IPILIMUMAB, NIVOLUMAB

A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients With Advanced Solid Tumors
NCT04317105

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
PIK3CA	Tier 2C Pathogenic	amplification	Timothy A Yap;

COPANLISIB, NIVOLUMAB

An Open-label, Multi-center, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Copanlisib in Combination With Nivolumab in Patients With Advanced Solid Tumors.
NCT03735628

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, CO, OH, RI
PIK3CA	Tier 2C Pathogenic	amplification	Bayer Clinical Trials Contact; clinical-trials-contact@bayer.com; (+)1-888-84 22937;

Phase 1 clinical trials (17)

BAY1905254

An Open-label, Phase 1, First-in-human, Dose Escalation and Expansion Study to Evaluate the Safety, Tolerability, Maximum Tolerated or Administered Dose, Pharmacokinetics, Pharmacodynamics and Tumor Response Profile of the ILDR2 Function-blocking Antibody BAY1905254 in Patients With Advanced Solid Tumors
NCT03666273

Qualifying variant			Contact
Biomarker	Classification	Score	United States: CT, IL, MI, TX
TMB-high	Tier 1A Pathogenic	56.3 Mutations/Megabase	Bayer Clinical Trials Contact; clinical-trials-contact@bayer.com; (+)1-888-8422937;

GLS-010

A Phase 1b Study to Evaluate the Safety and Clinical Activity of AB122 in Biomarker-Selected Participants With Advanced Solid Tumors
NCT04087018

Qualifying variant			Contact
Biomarker	Classification	Score	United States: AL, CA, DE, KY, LA, MD, MN, OH, PA, SC, WA, WI
TMB-high	Tier 1A Pathogenic	56.3 Mutations/Megabase	Medical Director; ClinicalTrialInquiry@arcusbio.com; 510-694-6200;

IPILIMUMAB, KRAS PEPTIDE VACCINE, NIVOLUMAB

Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected MMR-p Colorectal and Pancreatic Cancer
NCT04117087

Qualifying variant			Contact
Gene	Classification	Variant	United States: MD
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A	Susan Sartorius-Mergenthaler, RN; Sartosu@jhmi.edu; 410-614-3644;

PEMBROLIZUMAB, V 941

A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma
NCT03948763

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, CT, MA, NV, TN, TX, WA
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A	Toll Free Number; Trialsites@merck.com; 1-888-577-8839;

Phase 1 clinical trials (17)

RMC-4630
A Phase 1, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants With Relapsed/Refractory Solid Tumors
NCT03634982

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

Contact
United States: AZ, CA, CO, FL, MA, OK, TN, TX
Revolution Medicines, Inc.; CT-Inquiries@RevMed.com;
(650) 779-2300;

BCA101
First-in-Human, Phase 1/1b, Open-label, Multicenter Study of Bifunctional EGFR/TGFβ Fusion Protein BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-Driven Advanced Solid Tumors
NCT04429542

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12D c.35G>A

Contact
United States: TX
David Bohr, MS MPH MBA; david.bohr@bicara.com;
5166037631;

ABEXINOSTAT, PAZOPANIB
Phase I Study to Evaluate the Tolerability, Efficacy, and Safety of Pazopanib in Combination With PCI-24781 in Patients With Metastatic Solid Tumors
NCT01543763

Qualifying variants

Gene	Classification	Variant
FGFR3	Tier 2C Pathogenic	amplification
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

Contact
United States: CA
Pamela Munster, MD; Pamela.Munster@ucsf.edu;
(415) 502-3598;

CABOZANTINIB, DURVALUMAB
A Phase Ib Trial of Cabozantinib in Combination With Durvalumab (MEDI4736) in Previously Treated Patients With Advanced Gastroesophageal Cancer and Other Gastrointestinal (GI) Malignancies (CAMILLA)
NCT03539822

Qualifying variant

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification

Contact
United States: KS
Kerry Hepler; ctnursenav@kumc.edu;
913-945-7552;

SORAFENIB, DASATINIB, LENVATINIB, CABOZANTINIB, REGORAFENIB, IMATINIB, PONATINIB, SUNITINIB
Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) Trial: PRIME
NCT03878524

Qualifying variants

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification
PIK3CA	Tier 2C Pathogenic	amplification

Contact
United States: OR
Kiara Siex, MPH; siex@ohsu.edu;
503-418-3115;

IPILIMUMAB, IMATINIB
A Phase I Trial of Ipilimumab (Immunotherapy) and Imatinib Mesylate (c-Kit Inhibitor) in Patients With Advanced Malignancies
NCT01738139

Qualifying variants

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification
PDGFRA	Tier 2C Pathogenic	amplification

Contact
United States: TX
David Hong; dshong@mdanderson.org;
713-563-1930;

NILOTINIB, PACLITAXEL
Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults and Pediatiric Patients With Refractory Solid Tumors
NCT02379416

Qualifying variants

Gene	Classification	Variant
KIT	Tier 2C Pathogenic	amplification

Contact
United States: MD
Murielle Hogu; murielle.hogu@nih.gov;

Phase 1 clinical trials (17)

Gene	Classification	Variant	
PDGFRA	Tier 2C Pathogenic	amplification	(240) 858-3335;

COPANLISIB, NIVOLUMAB

Phase Ib Study of Copanlisib in Combination With Nivolumab or With Nivolumab and Ipilmumab
NCT03502733

Qualifying variant			Contact
Gene	Classification	Variant	United States: MD, TX
PIK3CA	Tier 2C Pathogenic	amplification	Geraldine O'Sullivan Coyne;

SERABELISIB, SAPANISERTIB, PACLITAXEL

A Phase 1 Evaluation of the Safety and Tolerability of TAK-228 in Combination With TAK-117 and Paclitaxel in Advanced Solid Tumors
NCT03154294

Qualifying variant			Contact
Gene	Classification	Variant	United States: SD
PIK3CA	Tier 2C Pathogenic	amplification	Casey Williams, PharmD; Casey.Williams@Avera.org; 605-322-3588;

GEDATOLISIB, PALBOCICLIB

Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors
NCT03065062

Qualifying variant			Contact
Gene	Classification	Variant	United States: MA
PIK3CA	Tier 2C Pathogenic	amplification	Geoffrey Shapiro, MD; Geoffrey_Shapiro@dfci.harvard.edu; 617-632-4942;

AMG 650

A Phase 1, Multicenter, Open-label, Dose-Exploration and Dose-Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 650 in Subjects With Advanced Solid Tumors
NCT04293094

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, IN, MO, NY, TN, TX
TP53	Tier 2C Pathogenic	p.P278S c.832C>T	Amgen Call Center; medinfo@amgen.com; 866-572-6436;

COTI-2, CISPLATIN

A Phase 1 Study of COTI-2 as Monotherapy or Combination Therapy for the Treatment of Advanced or Recurrent Malignancies
NCT02433626

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
TP53	Tier 2C Pathogenic	p.P278S c.832C>T	Richard Ho, MD-PhD; rho@cotingapharma.com;

BI754111, BI 907828, BI 754091

A Phase Ia/Ib, Open Label, Dose-escalation Study of the Combination of BI 907828 With BI 754091 and BI 754111, Followed by Expansion Cohorts, in Patients With Advanced Solid Tumors
NCT03964233

Qualifying variant			Contact
Gene	Classification	Variant	United States: CT, NY, TX
TP53	Tier 2C Pathogenic	p.P278S c.832C>T	Boehringer Ingelheim; clintriage.rdg@boehringer-ingelheim.com; 1-800-243-0127;

Early Phase 1 clinical trials (1)

PEMBROLIZUMAB

A Single-Arm Pilot Study of Adjuvant Pembrolizumab in Patients With MSI-H Tumors With Persistent Circulating Tumor DNA Following Surgery
NCT03832569

Early Phase 1 clinical trials (1)

Qualifying variant

Biomarker	Classification	Score
MSI-high	Tier 1A Pathogenic	-

Contact

United States: NJ, NY
Yelena Janjigian, MD; janjigiy@mskcc.org;
646-888-4186;

VARIANT DETAILS

Biomarkers (2)

Tumor Mutation Burden: TMB-high (56.3 Mutations/Megabase)

Biomarker: TMB-high
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Sensitive
4 Trials

Biomarker summary: Tumor Mutational Burden-high is an activating mutation.

Clinical relevance: Deregulation of multiple cellular processes is capable of introducing DNA alterations during tumorigenesis. Genetic mutations in tumor cells have been reported to result in the production of neoantigens, which are immunogenic peptides recognized by tumor-infiltrating lymphocytes (TILs) [229, 7, 352, 118]. Studies have shown high tumor mutational burden or high levels of neoantigens to be associated with high expression of cytotoxic T-cell markers; thus, immunotherapies may be relevant in tumors with high tumor mutational burden [148, 118, 40, 331]. Indeed, high tumor mutational burden has been associated with increased clinical benefit of several immune checkpoint inhibitors, including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and atezolizumab in studies of NSCLC, urothelial carcinoma, and other solid tumors [329, 42, 115, 327, 109, 138, 462, 333, 166, 121, 343]. Pembrolizumab has been FDA-approved for the treatment of pediatric and adult solid tumors with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase as determined by an approved test.

Disease summary: High mutational burden has been associated with microsatellite instability (MSI) and mismatch-repair deficiency (MMR-D) in studies of colorectal carcinoma [377, 224, 204, 44, 98, 205]. In one Phase 2 study of the PD-1 inhibitor pembrolizumab in 41 patients with colorectal carcinoma, higher somatic mutation load was significantly associated with longer progression-free survival and associated with a trend towards improved response rate [204].

Molecular function: A test result demonstrating high tumor mutational burden has been reported in this sample.

Incidence: Hypermutation has been reported in 2-18% of colorectal carcinoma (CRC) samples analyzed in literature studies [44, 85].

Role in disease: Multiple mechanisms, including oncogene-induced replication stress and deregulation of DNA replication, have been reported to introduce DNA alterations during tumorigenesis, resulting in variable frequencies of somatic mutations in different cancer subtypes [229, 7]. Genetic mutations in tumor cells can result in the production of neoantigens, which are presented in context of MHC molecules on cancer cells to tumor-infiltrating lymphocytes (TILs) [118, 352, 331]. High mutational burden has been associated with microsatellite instability (MSI) and mismatch-repair deficiency (MMR-D) in studies of colorectal carcinoma [377, 224, 204, 44, 98, 205].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Studies have shown high tumor mutational burden or high levels of neoantigens to be associated with high expression of cytotoxic T-cell markers; thus, immunotherapies may be relevant in tumors with high tumor mutational burden [148, 118, 40, 331]. A large study of advanced cancer patients reported that higher tumor mutation burden (TMB, defined as the highest 20% in each histology) was associated with significantly increased survival in patients treated with a variety of immune checkpoint inhibitors, although the numeric cutoff for TMB in each histology was highly variable. Tumor types with the most significant improvement were bladder, colorectal, head and neck, melanoma, and NSCLC. Breast cancer and glioma with high TMB were not associated with increased survival [343]. Pembrolizumab has been FDA-approved for the treatment of pediatric and adult solid tumors with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase as determined by an approved test. In one Phase 2 study of pembrolizumab in 41 patients with colorectal carcinoma, higher somatic mutation load was significantly associated with longer progression-free survival and associated with a trend towards improved response rate [204].

Drug resistance: None.

Approved Drugs: Pembrolizumab.

Biomarkers (2)

Phase 3: Preliminary presentation of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 metastatic colorectal carcinoma patients having tumors with high microsatellite instability (MSI-H) or deficient in mismatch repair (dMMR) has reported progression-free survival and confirmed overall response rate of 16.5 months and 43.8% with pembrolizumab and 8.2 months and 33.1% with chemotherapy; the median duration of response was not reached with pembrolizumab and was 10.6 months with chemotherapy. Serious adverse events (Grade 3-5) were reported in 22% and 66% of patients treated with pembrolizumab and chemotherapy, respectively [1]. A Phase 3 trial (IMblaze370) of atezolizumab with cobimetinib (AC), atezolizumab monotherapy (AM), or regorafenib in patients with metastatic colorectal carcinoma reported median overall survival of 8.87, 7.1, and 8.51 months in the AC, AM, and regorafenib arms, respectively. Treatment-related grade 3-4 adverse events were reported in 61% (109 /179), 31% (28/90), and 58% (46/80), respectively [94].

Phase 2: A Phase 2 trial of pembrolizumab with cyclophosphamide and the colon vaccine GVAX in 17 patients with advanced MMR-proficient colorectal carcinoma reported disease control rates of 18% and 29% by RECIST and irRC, respectively. No objective responses were reported; median progression-free and overall survival were 2.7 and 7.1 months. Grade 3-4 adverse events attributed to study therapy were reported in 11.8% (2/17) of patients [463]. A Phase 2 study of nivolumab in 74 dMMR or MSI-H CRC patients has reported investigator and independent radiology review committee objective response rates of 27% and 31% and disease control rates of 62% and 69% with a time to response of approximately 2.7 months; progression-free survival rates at 12 months were 46% and 48% with 83.4% overall survival at six months and 73.8% at 12 months [286]. A Phase 2 study of nivolumab with ipilimumab in 40 patients with MSS colorectal adenocarcinoma reported a disease control rate of 25%, and an objective response rate of 10% by intent to treat analysis [PMID:32085022]. A Phase 2 trial of durvalumab with tremelimumab (DT) plus best supportive care (BSC) or BSC alone in 179 patients with advanced/refractory colorectal carcinoma reported median progression-free survival of 1.8 and 1.0 months, and median overall survival of 6.6 and 4.1 months in the DT+BSC and BSC alone arms, respectively. Disease control rates were 22.7% and 6.6%, respectively. The Phase 2 AVETUX study of avelumab plus cetuximab in combination with FOLFOX in 39 previously untreated metastatic colorectal cancer patients has reported overall response rate of 79.5%, with six complete and 25 partial responses, and disease control rate of 92.3%.

Phase 1: A Phase 1b trial of atezolizumab in combination with bevacizumab in refractory metastatic colorectal cancer patients reported an unconfirmed overall response rate (ORR) of 8% (1/13) and grades 3/4 adverse events in 64% of cases. In oxaliplatin-naïve patients treated with atezolizumab in combination with bevacizumab and FOLFOX, the unconfirmed ORR in evaluable patients was 36% (9/25), with 73% of cases reporting grades 3/4 adverse events. A Phase 1b trial of atezolizumab in combination with bevacizumab in microsatellite instability (MSI)-high metastatic colorectal cancer patients has reported partial response in 30% (3/10) and stable disease in 60% (6/10) of patients. Grade 3/4 adverse events were observed in 40% of patients. An ongoing Phase 1b trial of atezolizumab in combination with cobimetinib in 84 chemotherapy-refractory or locally advanced metastatic colorectal cancer patients has reported an overall response rate of 8%, including patients with MSS and MSI-low status, and disease control rate of 31%, with median progression-free and overall survival of 1.9 and 10.0 months, respectively. A Phase 1 study of durvalumab plus monalizumab in 55 solid tumor patients has reported confirmed partial response in three and stable disease in 11 patients in the expansion cohort of 40 metastatic microsatellite-stable colorectal cancer patients, with disease control rate at 16 weeks of 24%. A Phase 1 study of oleclumab and durvalumab in 66 solid tumor patients, with an expansion cohort in 41 advanced microsatellite-stable colorectal cancer (MSS-CRC) and pancreatic cancer patients has reported partial response in 5% (1/21) and 10% (2/20), and stable disease in 10% (2/21) and 15% (3/20) of MSS-CRC and pancreatic cancer patients, respectively.

Preclinical: N/A: Preclinical data are not presented when higher level data are available.

Microsatellite Status: MSI-high

Biomarker: MSI-high
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
3 Sensitive
10 Trials

Biomarker summary: MSI-high instability exhibits altered function compared to wild-type.

Clinical relevance: Tumors exhibiting microsatellite instability (MSI) have a higher mutational burden than microsatellite stable (MSS) tumors and express higher levels of immune checkpoint receptors [181, 6, 148, 413, 234]. Thus, checkpoint inhibitors, several of which have received agency approval for certain indications, may be clinically relevant for tumors exhibiting MSI [260, 415, 289, 405, 204, 438]. In fact, pembrolizumab has been FDA-approved as a second or later line of therapy for the treatment of pediatric and adult solid tumors with high microsatellite instability (MSI-H) or that are deficient in mismatch repair (dMMR) and as a front-line therapy for colorectal carcinoma patients with MSI-H or dMMR [211, 204]. In addition, nivolumab and the combination of nivolumab and ipilimumab have been FDA-approved for the treatment of MSI-H or dMMR colorectal carcinoma [285, 286].

Biomarkers (2)

Disease summary: MSI has been associated with proximal colon location, mucinous histology, lower tumor grade, age at diagnosis of less 50 years old, and the presence of BRAF mutation in colorectal carcinoma studies [369, 410, 48, 113, 16]. Adjuvant 5FU may not benefit colorectal cancer patients with stage II/III MSI-H tumors when given as monotherapy [326, 346, 402].

Molecular function: The revised Bethesda Guidelines recommended criteria for defining a tumor with high microsatellite instability (MSI-H) include detecting alterations in two or more of the five microsatellite markers included in the National Cancer Institute (NCI) microsatellite panel [33, 422].

Incidence: MSI has been reported in 4-24% of colorectal carcinoma samples and has been observed in both inherited and sporadic forms of the disease [120, 393, 240, 52, 369, 278, 309, 137, 394, 113].

Role in disease: MSI is associated with the loss or dysfunction of DNA mismatch repair (MMR) proteins that are required for correcting errors that occur during DNA replication or recombination; germline mutations in genes encoding MMR proteins are associated with Lynch syndrome, a hereditary cancer-predisposition syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC) [241, 61, 137]. Tumors exhibiting MSI have been reported to have increased numbers of tumor-infiltrating lymphocytes (TILs) and a significantly higher mutational burden than microsatellite stable (MSS) tumors [181, 6, 148, 413]. MSI has been associated with proximal colon location, mucinous histology, lower tumor grade, age at diagnosis of less 50 years old, and the presence of BRAF mutation in colorectal carcinoma studies [369, 16, 410, 48, 113]. In addition, increased frequency of PD-L1 expression has been reported in colorectal carcinoma cases with MSI-H as compared with MSS/MSI-L cases [197, 423, 342, 208].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: MSI has been reported to correlate with high levels of immune checkpoint gene expression in some types of cancer, including colorectal and endometrial carcinoma, and with clinical response to checkpoint inhibition in colorectal carcinoma; thus, immunotherapies may be relevant in tumors exhibiting MSI [234, 204, 148]. Checkpoint inhibitors are currently in clinical development, several of which have received agency approval for certain indications [260, 438]. In fact, pembrolizumab has been FDA-approved as a second or later line of therapy for the treatment of pediatric and adult solid tumors with high microsatellite instability (MSI-H) or that are deficient in mismatch repair (dMMR) and as a front-line therapy for colorectal carcinoma patients with MSI-H or dMMR [211, 204]. In addition, nivolumab and the combination of nivolumab and ipilimumab have been FDA-approved for the treatment of MSI-H or dMMR colorectal carcinoma [285, 286]. A Phase 1 follow-up study of nivolumab in 39 treatment-refractory solid tumor patients reported that one patient with MSI-H colorectal cancer showed an ongoing complete response of at least three years [230].

Drug resistance: Adjuvant 5FU may not benefit colorectal cancer patients with stage II/III MSI-H tumors when given as monotherapy [326, 346, 402]. The therapeutic implications of MLH1 mutation or hypermethylation have been best studied in colon cancer. High MSI has been associated with lack of benefit from 5-FU based regimens [326, 346, 402, 136].

Approved Drugs: Ipilimumab. Nivolumab. Pembrolizumab.

Phase 3: Preliminary presentation of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 metastatic colorectal carcinoma patients having tumors with high microsatellite instability (MSI-H) or deficient in mismatch repair (dMMR) has reported progression-free survival and confirmed overall response rate of 16.5 months and 43.8% with pembrolizumab and 8.2 months and 33.1% with chemotherapy; the median duration of response was not reached with pembrolizumab and was 10.6 months with chemotherapy. Serious adverse events (Grade 3-5) were reported in 22% and 66% of patients treated with pembrolizumab and chemotherapy, respectively [1]. A Phase 3 trial (IMblaze370) of atezolizumab with cobimetinib (AC), atezolizumab monotherapy (AM), or regorafenib in patients with metastatic colorectal carcinoma reported median overall survival of 8.87, 7.1, and 8.51 months in the AC, AM, and regorafenib arms, respectively. Treatment-related grade 3-4 adverse events were reported in 61% (109 /179), 31% (28/90), and 58% (46/80), respectively [94].

Phase 2: A Phase 1/2 study of durvalumab monotherapy in 62 patients with MSI-high solid tumors, including 36 patients with colorectal carcinoma (CRC), 17 patients with endometrial carcinoma, and 9 patients with other tumor types, has reported an objective response rate of 23% and 22% for all patients and CRC patients, respectively; treatment-related adverse events (TRAEs) were reported in 60% (37/62) of patients, including grade 3/4 TRAEs in 3% (2/62) of cases. Long-term followup of the Phase 2 CheckMate 142 study of nivolumab plus ipilimumab in dMMR or MSI-H CRC patients who had received at least one prior therapy reported an investigator-assessed overall response rate of 58% and a disease control rate of 81% at a median followup of 25.4 months. Complete and partial responses were reported in 6% (7/119) and 52% (62/119) of patients; median progression-free and overall survival rates at 24 months were 60% and 74%. Grade 3-4 adverse

Biomarkers (2)

events were reported in 31% of patients. A Phase 2 study of nivolumab plus ipilimumab with radiotherapy in 40 metastatic microsatellite stable colorectal carcinoma (CRC) patients and 25 metastatic pancreatic ductal adenocarcinoma (PDAC) patients with progression on previous lines of therapy has reported disease control in 25% (10/40) and 20% (5/25), and overall response in 10% (4/40) and 13% (3/25) of patients in the CRC and PDAC cohorts, respectively. Grade 3 or higher treatment-related adverse events were observed in 40% (26 /65) of patients, with grade 5 events in 3.1% (2/65) of patients [PMID:32085022]. A Phase 2 study of nivolumab in 74 dMMR or MSI-H CRC patients has reported investigator and independent radiology review committee objective response rates of 27% and 31% and disease control rates of 62% and 69% with a time to response of approximately 2.7 months; progression-free survival rates at 12 months were 46% and 48% with 83.4% overall survival at six months and 73.8% at 12 months [286]. A Phase 2 study of nivolumab with ipilimumab in 40 patients with MSS colorectal adenocarcinoma reported a disease control rate of 25%, and an objective response rate of 10% by intent to treat analysis [PMID:32085022]. A Phase 2 trial of pembrolizumab with cyclophosphamide and the colon vaccine GVAX in 17 patients with advanced MMR-proficient colorectal carcinoma reported disease control rates of 18% and 29% by RECIST and irRC, respectively. No objective responses were reported; median progression-free and overall survival were 2.7 and 7.1 months. Grade 3-4 adverse events attributed to study therapy were reported in 11.8% (2/17) of patients [463]. A Phase 2 trial of durvalumab with tremelimumab (DT) plus best supportive care (BSC) or BSC alone in 179 patients with advanced/refractory colorectal carcinoma reported median progression-free survival of 1.8 and 1.0 months, and median overall survival of 6.6 and 4.1 months in the DT+BSC and BSC alone arms, respectively. Disease control rates were 22.7% and 6.6%, respectively. The Phase 2 AVETUX study of avelumab plus cetuximab in combination with FOLFOX in 39 previously untreated metastatic colorectal cancer patients has reported overall response rate of 79.5%, with six complete and 25 partial responses, and disease control rate of 92.3%.

Phase 1: A safety and efficacy study of pembrolizumab in 149 patients with tumors with high microsatellite instability (MSI-H) or deficient in mismatch repair (dMMR) across five Phase 1 and 2 uncontrolled trials and including 15 different cancer types has reported a complete or partial response in 39.6% of patients; 78% of patients experienced response for six months or more (FDA press announcement) [211, 204]. A Phase 2 study of pembrolizumab in patients with advanced dMMR cancers, including 12 different tumor types, has reported complete and partial responses in 23.1% (18/78) and 35.9% (28/78) of evaluable patients, respectively [203]. A Phase 1b trial of atezolizumab in combination with bevacizumab in refractory metastatic colorectal cancer patients reported an unconfirmed overall response rate (ORR) of 8% (1/13) and grades 3/4 adverse events in 64% of cases. In oxaliplatin-naïve patients treated with atezolizumab in combination with bevacizumab and FOLFOX, the unconfirmed ORR in evaluable patients was 36% (9/25), with 73% of cases reporting grades 3/4 adverse events. A Phase 1b trial of atezolizumab in combination with bevacizumab in microsatellite instability (MSI)-high metastatic colorectal cancer patients has reported partial response in 30% (3/10) and stable disease in 60% (6/10) of patients. Grade 3/4 adverse events were observed in 40% of patients. An ongoing Phase 1b trial of atezolizumab in combination with cobimetinib in 84 chemotherapy-refractory or locally advanced metastatic colorectal cancer patients has reported an overall response rate of 8%, including patients with MSS and MSI-low status, and disease control rate of 31%, with median progression-free and overall survival of 1.9 and 10.0 months, respectively. A Phase 1 study of durvalumab plus monalizumab in 55 solid tumor patients has reported confirmed partial response in three and stable disease in 11 patients in the expansion cohort of 40 metastatic microsatellite-stable colorectal cancer patients, with disease control rate at 16 weeks of 24%. A Phase 1 study of oleclumab and durvalumab in 66 solid tumor patients, with an expansion cohort in 41 advanced microsatellite-stable colorectal cancer (MSS-CRC) and pancreatic cancer patients has reported partial response in 5% (1/21) and 10% (2/20), and stable disease in 10% (2/21) and 15% (3/20) of MSS-CRC and pancreatic cancer patients, respectively.

Preclinical: N/A: Preclinical data are not presented when higher level data are available.

Variant of strong clinical significance (1)

KRAS G12D

Gene: KRAS
Exon: 2
Nucleotide:
NM_004985.5:
g.25398284C>T
c.35G>A
Amino Acid: p.G12D
Allelic Fraction: 20.0% (of 243 reads)
Classification: Tier 1A
Assessment: Pathogenic

Biomarker summary: KRAS-G12D is an activating mutation.

Clinical relevance: KRAS encodes the signaling protein K-Ras, a member of the Ras family; activating KRAS alterations may result in activation of downstream signaling pathways, including the Raf/MEK/ERK pathway [316, 274]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [169, 3, 249, 155, 231, 143, 30, 473]. Other clinical approaches are also under investigation in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors [117, 246, 338, 194, 403, 53]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [227, 159, 283, 297].

Disease summary: Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the

Variant of strong clinical significance (1)

Treatment options
2 Resistance
9 Trials

development and progression of colorectal cancer [73, 41, 416, 35]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, the NCCN guidelines (v.4.2020) recommend against the use of cetuximab and panitumumab.

Molecular function: KRAS G12D is a missense alteration within the first "G box" domain of the K-Ras protein, one of several conserved regions responsible for GTP binding and hydrolysis; disruption of this region creates a protein that is defective for GTP hydrolysis and is therefore constitutively active [255, 267, 63]. KRAS G12D has been shown to be an oncogenic mutation, inducing tumor formation and metastasis in mice [280, 168, 318, 158].

Incidence: KRAS mutations have been reported in 35% (21868/63189) of Colorectal adenocarcinoma samples analyzed in COSMIC (May 2020). KRAS mutations have been reported in 41-55% of Colorectal adenocarcinoma samples (cBioPortal for Cancer Genomics, May 2020). KRAS mutations have been reported in 30-49% of colorectal cancer samples analyzed in scientific studies; however, many studies have only assayed for KRAS mutational hotspots, such as codons 12 and 13 [119, 288, 365, 472, 457, 299, 195, 112, 179, 9, 101].

Role in disease: The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers [100, 104, 135]. Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer [73, 35].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf/MEK/ERK and PI3K/Akt/mTOR [464, 38]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [169, 3, 249, 155, 231, 143, 30, 473]. One clinical approach for KRAS-positive tumors, based on synthetic lethal interactions that occur in the presence of a KRAS mutation and either diminished Cdk4 activity or diminished Bcl-2/Bcl-xL activity, is a treatment combination of MEK inhibition and either Cdk4/6 inhibition or Bcl-2/Bcl-xL inhibition [251, 315, 401, 64]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors [117, 246, 338, 194, 403, 53]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [227, 159, 283, 297].

Drug resistance: In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies [101, 91, 226, 321, 43, 75, 87, 424, 219]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, the NCCN guidelines (v.4.2020) recommend against the use of cetuximab and panitumumab.

Approved Drugs: None.

Phase 3: A Phase 3 trial (IMblaze370) of atezolizumab with cobimetinib (AC), atezolizumab monotherapy (AM), or regorafenib in patients with metastatic colorectal carcinoma reported median overall survival of 8.87, 7.1, and 8.51 months in the AC, AM, and regorafenib arms, respectively. Treatment-related grade 3-4 adverse events were reported in 61% (109/179), 31% (28/90), and 58% (46/80), respectively [94].

Phase 2: A Phase 2 trial of selumetinib in patients with KRAS-mutant colorectal carcinoma who were progressing on first-line therapy reported partial response and stable disease lasting at least four weeks in 9.7% (3/31) and 51.6% (16/31) of patients, respectively; notably, three patients were reported to have stable disease lasting more than one year [143]. A Phase 2 clinical trial of temsirolimus as a single agent or in combination with irinotecan in patients with KRAS-mutant CRC has reported stable disease in 38% (24/64) and 63% (40/63) of patients on monotherapy or combination therapy, respectively; however, all patients who exhibited tumor reduction were found to have low levels of mutated KRAS in plasma samples [373]. A Phase 2 study which compared selumetinib with capecitabine as monotherapy in colorectal cancer patients reported stable disease in 29% (10/34) of patients in the selumetinib group as compared to 43% (15/35) in the capecitabine group. No significant differences in progression-free survival times or in the number of patients with disease progression were reported [27].

Phase 1: A retrospective study of bevacizumab in 404 metastatic CRC patients reported that median progression-free and overall survival rates for patients harboring KRAS G12A/V mutations (6.6 and 16.8 months, respectively) were significantly lower than for patients harboring other KRAS mutations (16.8 and 26.3

Variant of strong clinical significance (1)

months, respectively) [105]. A study of mirdametinib (PD0325901) in 13 patients with metastatic tumors (seven melanoma, three breast, and three colorectal cases) reported clinical benefit in six patients (one confirmed complete response in a melanoma case as well as five patients with stable disease). However, the drug was not well tolerated at the doses administered and the study was terminated early [32]. A Phase 1 multicenter trial of refametinib in 53 patients with advanced cancer reported suppression of ERK phosphorylation and stable disease in 11 patients for four or more courses of therapy [442]. A Phase 1 study of refametinib in combination with sorafenib in 54 patients with advanced solid tumors reported, in 38 non-hepatocellular carcinoma (non-HCC) patients evaluable for response, a partial response lasting approximately one year in a colorectal carcinoma patient and stable disease in 63.2% (24/38) of patients; treatment was associated with a reduction in ERK activation in five of six non-HCC biopsied cases [4]. A case study has reported that a patient with MEK1 mutant-positive metastatic colon cancer progressed on chemotherapy, trametinib, ulixertinib, and ulixertinib in combination with panitumumab; a temporary decrease in CA19.9 tumor marker was observed following trametinib and ulixertinib treatments [435]. A Phase 1 study of binimetinib in 93 patients with advanced solid tumors, with expansion cohorts of biliary cancer and KRAS or BRAF-mutant colorectal carcinoma, has reported one complete response, two partial responses, and 33 stable diseases in 91 evaluable patients; all three objective responses were patients with biliary cancer [25]. A Phase 1 study of binimetinib continuous dosing combined with FOLFOX in advanced metastatic colorectal cancer patients has reported stable disease at two months in 69% (9/13) of patients [57]. In a Phase 1 trial of the MEK inhibitor trametinib in patients with advanced solid tumors, an overall 10% objective response rate was reported. No objective responses were seen in 28 patients with colorectal cancer, although nine patients had stable disease [153]. A Phase I trial of trametinib in combination with 5-fluorouracil chemoradiation in 18 evaluable patients with locally advanced rectal cancer has reported a pathological complete response in 17% (3/18) of patients [452]. A Phase 1b trial of cobimetinib in combination with atezolizumab in 84 colorectal cancer patients, including 57 with KRAS-mutant and 25 KRAS wild-type, reported partial response in 8.3% (7/84) of patients, with a median progression-free survival and overall survival of 1.9 and 10.0 months, respectively; grades 3/4 related adverse events occurred in 37% of patients.

Preclinical: Preclinical studies have reported that treatment of KRAS-mutant colorectal cancer (CRC) models with a MEK inhibitor (binimetinib or trametinib) combined with a Cdk4/6 inhibitor (palbociclib) resulted in greater cell growth inhibition in vitro and greater anti-tumor activity in vivo, in colorectal cancer cell lines and patient-derived xenograft models, than either treatment alone [475, 209]. Preclinical studies suggest that combinations of MEK and PI3K inhibitors may result in synergistic cytotoxicity and/or tumor regression in colorectal cancer cell and animal models, though strategies that enhance tumor specific delivery may be required to overcome systemic toxicity [374, 332, 261]. A preclinical study reported that lenvatinib inhibited tumor growth and reduced tumor-associated vessel density in KRAS mutant colorectal carcinoma xenograft models [448]. One preclinical study of colorectal cancer cell lines and mouse xenograft models of colorectal cancer that exhibited primary or acquired resistance to cetuximab reported that combined cetuximab and refametinib treatment resulted in significantly increased growth inhibition as compared with treatment using cetuximab alone [417].

Variants of potential clinical significance (6)

FGFR3 amplification

Gene: FGFR3
Amino Acid: amplification
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
10 Trials

Biomarker summary: FGFR3-amplification is predicted to be an activating alteration.

Clinical relevance: FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor [310, 97]. Tumors with FGFR3 amplification or activating mutations may be sensitive to Fgfr inhibitors. Tyrosine kinase inhibitors whose targets include Fgfrs have been approved for some tumor types and clinical trials of these agents and other agents targeting Fgfrs are ongoing in solid tumors [349, 482, 379, 268, 66]. Erdafitinib has been FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after at least one line of platinum-containing chemotherapy and have a susceptible FGFR3 or FGFR2 alteration.

Disease summary: Fgfr3 signaling in a colon cancer cell line has been associated with increased cell migration and invasion in one study [139]. Overexpression of Fgfr3 has been reported to induce resistance to irinotecan in colorectal carcinoma cells in one preclinical study [96].

Molecular function: FGFR3 amplification has been reported in several tumor types and has been associated with increased Fgfr3 protein expression in some cases [157, 317, 106, 312, 409]. Protein analysis may be considered to validate increased expression and/or activation of Fgfr3.

Incidence: Putative high-level amplification of FGFR3 has been reported in less than 1% (2/592) of Colorectal adenocarcinoma cases (Colorectal Adenocarcinoma (TCGA, PanCancer Atlas), cBioPortal for Cancer Genomics, May 2020). One study has reported no FGFR3 amplification in 80 colorectal cancer samples [111]. Decreased mean FGFR3 mRNA expression has been reported in 217 CRC samples as compared with matched normal tissue [362].

Variants of potential clinical significance (6)

Role in disease: Gain of function mutations in FGFRs have been reported in several cancer types [97, 447]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [421, 307, 222]. Fgfr3 signaling in a colon cancer cell line has been associated with increased cell migration and invasion in one study [139].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: FGFR3 amplification or mutations may lead to activation of Fgfr3 and may therefore confer sensitivity to Fgfr family inhibitors [421, 367]. Erdafitinib is a pan-FGFR inhibitor that has been FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after at least one line of platinum-containing chemotherapy and have a susceptible FGFR3 or FGFR2 alteration. Several multi-kinase inhibitors that target Fgfrs, including pazopanib, ponatinib, and lenvatinib, have been approved for certain indications and continue to be studied in clinical trials [349, 482, 379, 268, 66]. Additional agents that target Fgfrs are also being studied in clinical trials [279, 163, 425, 390, 322, 15].

Drug resistance: Overexpression of Fgfr3 has been reported to induce resistance to irinotecan in colorectal carcinoma cells in one preclinical study [96].

Approved Drugs: None.

Phase 3: A Phase 3 trial (LUME-Colon 1) of nintedanib or placebo plus best supportive care in 768 patients with metastatic colorectal cancer reported median progression-free survival of 1.5 and 1.4 months, and median overall survival of 6.4 and 6.0 months, respectively. Nintedanib was reported to be well tolerated [426].

Phase 2: A Phase 2 study of lenvatinib in 30 metastatic colorectal carcinoma patients refractory to standard chemotherapy has reported response rate of 6.7%, all partial responses, and disease control rate of 70.0% with median PFS of 3.6 months. A Phase 2 basket trial of infigratinib (BGJ398) monotherapy in patients with solid tumors harboring FGFR or FGF alterations has reported a clinical benefit rate at 16 weeks of 14.6%, including partial responses in 13.4% (11/82) of patients [363]. Results from a Phase 2 study of AZD4547 in FGFR-amplified advanced cancers reported responses in 33% (3/9) of FGFR2-amplified gastroesophageal cancer and 12.5% (1/8) of FGFR1-amplified breast cancer; all gastroesophageal cancer patients achieving a partial response had elevated FGFR2 copy number in free plasma DNA, which was not detected in patients without a response [298]. Preliminary analysis from the AZD4547 arm of the Phase 2 MATCH trial reported partial response in 5%, stable disease in 51%, and progressive disease in 44% of 41 evaluable solid tumor patients with an FGFR1-3 alteration. Partial responses occurred in patients with FGFR fusions (urothelial and cervical squamous cell carcinoma) and the six-month progression-free survival rate was highest (42%) in patients with FGFR fusions.

Phase 1: An interim analysis of the Phase 1 FIGHT-101 trial of pemigatinib in solid tumor patients reported partial responses in 12% (3/26) of patients harboring FGF/FGFR alterations, all in cholangiocarcinoma cases, as well as stable disease in 35% (9/26) of patients, while another arm with no selection for FGF/ FGFR status reported stable disease in 9/17 patients. Fatigue was reported as the most common treatment-emergent adverse event, arising in 10% of cases. A Phase 1 study of pazopanib plus gemcitabine in 22 patients with advanced solid tumors reported that the combination was well tolerated; in this study, a partial response was observed in a melanoma patient and stable disease for at least 12 treatment cycles was observed in three patients (one each with cholangiocarcinoma, melanoma, and colorectal cancer) [308]. A Phase 1 study of colorectal cancer patients treated with pazopanib in combination with either FOLFOX6 (20 patients) or CapeOx (21 patients) reported an overall response rate of 40% and 38% with these therapy combinations, respectively [36]. A Phase 1 study of lenvatinib in combination with capecitabine and radiation in 20 patients with locally advanced rectal adenocarcinoma has reported a pathological complete response in 29.4% (5/17) and downstaging in 71% (12/17) of evaluable patients. No grade 4 adverse events were observed. A Phase 1 study of erdafitinib in solid tumors and lymphoma has reported a manageable safety profile with four confirmed and one unconfirmed responses in 23 evaluable patients with FGFR pathway alterations, in patients with glioblastoma, urothelial, and endometrial carcinoma; 16 patients had stable disease [390]. A Phase 1 study of infigratinib (BGJ398) in 132 patients with advanced solid tumors harboring FGFR alterations reported seven partial responses, including partial responses in 11% (4/36) of FGFR1-amplified lung squamous cell carcinoma patients and 37.5% (3/8) of FGFR3-mutated urothelial carcinoma patients. Additionally, the safety profile of infigratinib was reported to be tolerable and manageable [279].

Preclinical: Preclinical studies have reported that ponatinib treatment reduced proliferation, growth, and migration in cell and mouse xenograft models of colorectal cancer [399, 8]. In addition, ponatinib treatment has been reported to result in inhibition of tumor growth in one of two colorectal carcinoma cell models without RET fusions. The effects of ponatinib were significantly enhanced in two colorectal carcinoma cell models harboring RET fusions [124]. Infigratinib (BGJ398) was reported to show dose-dependent inhibition of colorectal cancer

Variants of potential clinical significance (6)

cell lines and had a synergistic effect on induction of apoptosis in a colorectal carcinoma cell line when combined with either 5-fluorouracil or oxaliplatin chemotherapy [420]. In a preclinical study, treatment with AZD4547 inhibited tumor cell growth in colorectal cancer cell lines and a xenograft model that expressed Fgfr1 and Fgfr2 [461].

KIT amplification

Gene: KIT
Amino Acid: amplification
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
2 Resistance
9 Trials

Biomarker summary: KIT-amplification is an activating alteration.

Clinical relevance: Activating mutations in the Kit tyrosine kinase receptor lead to activation of downstream PI3K/Akt and Ras/MAPK signaling pathways, and may predict sensitivity to small molecule tyrosine kinase inhibitors [228, 90, 335, 389]. Several kinase inhibitors targeting Kit, including imatinib, sunitinib, and regorafenib, have been approved by the FDA in certain indications; others are under investigation in clinical trials [60, 167, 123, 31, 349].

Disease summary: Expression of Kit in colorectal cancer cells has been reported to increase cell proliferation and tumorigenesis and to correlate with markers of stemness [116, 359, 51]. Furthermore, decreased tumor proliferation and invasiveness have been reported in colorectal mucinous adenocarcinoma mouse models with a loss-of-function KIT mutation, as compared with KIT wild-type mice [400].

Molecular function: Amplification of KIT has been associated with expression of the Kit protein, and has been reported in multiple tumor types and correlated with tumorigenesis [314, 107, 392, 361, 150].

Incidence: Putative high-level amplification of KIT has been reported in less than 1% (1/592) of Colorectal adenocarcinoma cases (Colorectal Adenocarcinoma (TCGA, PanCancer Atlas), cBioPortal for Cancer Genomics, May 2020). A study reported KIT mutations in 8% of 112 colorectal carcinoma samples [162]. Expression of Kit has been reported in 2-17% of colon cancer samples analyzed in several studies; one study did not report Kit expression in any of the normal colonic mucosa or colonic adenoma samples [257, 323, 468, 108].

Role in disease: KIT is considered to be a proto-oncogene, and activating mutations of the KIT gene can lead to tumorigenesis [107]. Expression of Kit in colorectal cancer cells has been reported to increase cell proliferation and tumorigenesis and to correlate with markers of stemness [116, 359, 51]. Furthermore, decreased tumor proliferation and invasiveness have been reported in colorectal mucinous adenocarcinoma mouse models with a loss-of-function KIT mutation, as compared with KIT wild-type mice [400].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Activating mutations in KIT may predict sensitivity to small molecule tyrosine kinase inhibitors. Several tyrosine kinase inhibitors that target Kit, as well as other kinases, have received FDA approval in various tumor types. Other tyrosine kinase inhibitors are currently in clinical trials for patients with various solid tumors [265, 328, 349]. Additionally, the activation of Kit leads to activation of downstream pathways including MAPK, PI3K/Akt, STAT, and mTOR [90, 335, 389, 339]. Preclinical studies suggest that the combination of first-line kinase inhibitors with MEK, PI3K, mTOR, or Hsp90 inhibitors or new therapies, such as switch pocket kinase inhibitors, may be a useful strategy to target kinase inhibitor resistant tumors [366, 21, 180]. Regorafenib has been FDA-approved for the treatment of metastatic colorectal carcinoma (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and with an anti-EGFR therapy if wild-type for KRAS [127].

Drug resistance: None.

Approved Drugs: Regorafenib.

Phase 3: Regorafenib has been approved to treat patients with metastatic colorectal cancer based on the results of a trial (Study 14387) of 760 previously treated metastatic colorectal cancer patients; the study reported a significant increase in overall survival (6.4 months versus 5.0 months) and progression-free survival (1.9 months versus 1.7 months) in patients treated with regorafenib as compared with placebo [127]. A Phase 3 study of regorafenib versus placebo in 204 previously treated metastatic colorectal cancer patients of Asian origin reported a median overall survival of 8.8 months in the regorafenib arm (n=136) and 6.3 months in the placebo arm (n=68); adverse events were more frequently reported in the regorafenib arm compared to the placebo arm (97% vs. 46%) [218]. A Phase 3 clinical trial of 768 metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan (FOLFIRI), in combination with sunitinib, did not show significant clinical benefit; sunitinib in combination with FOLFIRI also showed a poor safety profile [46].

Variants of potential clinical significance (6)

Phase 2: A Phase 2 study of oxaliplatin, leucovorin, and fluorouracil in combination with sorafenib or placebo in metastatic colorectal cancer reported no benefit in terms of progression-free survival with the addition of sorafenib [391]. A Phase 1/2 trial of cabozantinib alone (C) or in combination with panitumumab (CP) in KRAS wild-type metastatic colorectal cancer patients reported partial response in 1/4 CP-treated patients. RECIST lesions were reduced in 1/3 patients receiving C, and in 3/4 patients receiving CP. Two Phase 2 trials evaluating the addition of axitinib to fluorouracil-based chemotherapy as first or second-line treatment of patients with metastatic colorectal cancer reported no improvement in progression-free survival or overall survival compared with bevacizumab with chemotherapy [154, 26]. A Phase 2 study of lenvatinib in 30 metastatic colorectal carcinoma patients refractory to standard chemotherapy has reported response rate of 6.7%, all partial responses, and disease control rate of 70.0% with median PFS of 3.6 months. A Phase 2 trial of dasatinib in 19 previously treated metastatic colorectal cancer patients was terminated due to lack of efficacy, with no objective responses, stable disease for 7.3 months in one patient, a progression-free survival (PFS) rate at four months of 5.3%, and a median PFS and overall survival of 1.6 and 5.1 months, respectively [355]. A Phase 1b/2 study of dasatinib with FOLFOX or cetuximab in 77 patients with previously treated KRAS codon 12/13 wild-type or mutant metastatic CRC, respectively, has reported response rates of 13% (3/24) and 0/23 in KRAS wild-type and mutant cohorts, respectively and a median progression-free survival of 2.3 months in both the KRAS wild-type and mutant cohorts [292]. A Phase 1/2 study examining imatinib in combination with capecitabine, oxaliplatin, and bevacizumab in 49 patients with CRC reported that 76% of patients were progression-free for at least six months [145].

Phase 1: A Phase 1 study of pazopanib plus gemcitabine in 22 patients with advanced solid tumors reported that the combination was well tolerated; in this study, a partial response was observed in a melanoma patient and stable disease for at least 12 treatment cycles was observed in three patients (one each with cholangiocarcinoma, melanoma, and colorectal cancer) [308]. A Phase 1 study of colorectal cancer patients treated with pazopanib in combination with either FOLFOX6 (20 patients) or CapeOx (21 patients) reported an overall response rate of 40% and 38% with these therapy combinations, respectively [36]. A Phase 1 study of lenvatinib in combination with capecitabine and radiation in 20 patients with locally advanced rectal adenocarcinoma has reported a pathological complete response in 29.4% (5/17) and downstaging in 71% (12 /17) of evaluable patients. No grade 4 adverse events were observed. Several Phase 1 studies have examined imatinib in combination with chemotherapy in colorectal cancer, and have reported efficacy; one study reported that 76% of patients (n=49) were progression-free for at least six months [259, 145, 178].

Preclinical: A preclinical study in a mouse xenograft model of colon cancer reported that nilotinib treatment led to decreased stromal reaction in the colon; a synergistic anti-tumor response was seen at the primary and metastatic tumor sites upon co-treatment with everolimus [471]. Preclinical studies have reported that ponatinib treatment reduced proliferation, growth, and migration in cell and mouse xenograft models of colorectal cancer [399, 8]. In addition, ponatinib treatment has been reported to result in inhibition of tumor growth in one of two colorectal carcinoma cell models without RET fusions. The effects of ponatinib were significantly enhanced in two colorectal carcinoma cell models harboring RET fusions [124].

NOTCH1 F357del

Gene: NOTCH1
Exon: 6
Nucleotide: NM_017617.5: g.139413070_139413072delAGA c.1070_1072delTCT
Amino Acid: p.F357del
Allelic Fraction: 11.0% (of 160 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Biomarker summary: NOTCH1-F357del is predicted to be an inactivating mutation.

Clinical relevance: Depending on cellular context, Notch1 can act as either a tumor suppressor or an oncogene [436, 189]. Activating NOTCH1 mutations stabilize the Notch1 intracellular protein and lead to increased Notch1 signaling [445]. Gamma-secretase inhibitors, which prevent cleavage of the intracellular domain, may be a potential therapeutic approach in the case of NOTCH1 activating mutations, and these are in clinical trials for various cancers [110, 126]. Some studies suggest that HDAC inhibitors, including panobinostat and valproic acid, may reactivate Notch pathway signaling in some tumors that have lost Notch expression through epigenetic silencing [92]. Inactivating NOTCH1 mutations have been reported to confer sensitivity to LGK974, a porcupine inhibitor currently under clinical investigation in solid tumors [232, 337]. While gamma-secretase inhibitors would not be expected to be relevant for this alteration, porcupine inhibitors may be a relevant therapeutic approach.

Disease summary: Notch1 overexpression has been reported to be involved in colorectal disease progression, cell proliferation, invasion and metastasis, although some studies have reported no association between overexpression and clinicopathological variables [216, 156, 217, 264, 220, 59, 360, 262].

Molecular function: NOTCH1 F357del is an in-frame deletion within the ninth EGF-like domain of the extracellular domain of the Notch1 protein (UniProt). Another alteration at this residue, NOTCH1 F357S, has been found in cancerous tissues of head and neck squamous cell carcinoma and has been predicted to influence the effectiveness of the calcium-dependent, ligand-binding functions of Notch1 protein [233, 65]. NOTCH1 F357del has been reported in a oligodendroglioma sample in one study and has also been reported 13 times in COSMIC (Jun 2019). Although it has not been functionally characterized (PubMed, Jun 2019), it is predicted to be inactivating [411].

Variants of potential clinical significance (6)

Incidence: NOTCH1 mutations have been reported in 7.3% (230/3171) of Colorectal adenocarcinoma samples analyzed in COSMIC (May 2020). NOTCH1 mutations have been reported in 0.7-8.3% of Colorectal adenocarcinoma samples (cBioPortal for Cancer Genomics, May 2020). NOTCH1 mutations have been reported in 1/653 and 1/112 colorectal carcinoma samples analyzed in two studies [247, 162].

Role in disease: Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [436, 189]. Notch1 overexpression has been reported to be involved in colorectal disease progression, cell proliferation, invasion and metastasis, although some studies have reported no association between overexpression and clinicopathological variables [216, 156, 217, 264, 220, 59, 360, 262].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Inactivating NOTCH1 mutations may result in Wnt pathway activation and a preclinical study associated NOTCH1 loss-of-function mutations with increased sensitivity to LGK974, a porcupine inhibitor currently in clinical trials in the context of cancer [232].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: A preclinical study of 40 head and neck squamous cell carcinoma cell lines reported that the presence of inactivating mutations in the N-terminal domain of NOTCH1 was associated with sensitivity to the porcupine inhibitor LGK974 [232]. A preclinical study has reported LGK974 to reduce metastatic spread of HNSCC cell lines, particularly in those harboring a NOTCH1 loss of function mutation [337]. In preclinical studies, LGK974 has been reported to inhibit colorectal carcinoma cell proliferation and tumor growth in models harboring Wnt pathway activating mutations [302].

PDGFRA amplification

Gene: PDGFRA
Amino Acid: amplification
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
1 Resistance
8 Trials

Biomarker summary: PDGFRA-amplification is an activating alteration.

Clinical relevance: PDGFRA encodes the tyrosine kinase receptor human platelet-derived growth factor receptor alpha, also known as Pdgfr-alpha (UniProt) [175]. PDGFRA amplification, overexpression, or activating mutation may predict sensitivity to small molecule tyrosine kinase inhibitors that target Pdgfrs as well as other kinases. Several kinase inhibitors have been approved for certain indications; others are under investigation in clinical trials [11, 176, 69]. Avapritinib has been FDA-approved for the treatment of GIST patients harboring PDGFR mutations in exon 18 [amino acids 814-854 (Integrative Genomics Viewer, v.2.8)].

Disease summary: High expression of PDGFRA mRNA and Pdgfr-alpha protein have been reported in colorectal cancer samples, and Pdgfr-alpha protein expression has been correlated with tumor stage and lymph node metastasis [348, 444].

Molecular function: Amplification of PDGFRA has been associated with expression of the Pdgfr-alpha protein, and has been reported in multiple tumor types and correlated with tumorigenesis [301, 47, 444, 348, 5].

Incidence: Putative high-level amplification of PDGFRA has been reported in less than 1% (2/592) of Colorectal adenocarcinoma cases (Colorectal Adenocarcinoma (TCGA, PanCancer Atlas), cBioPortal for Cancer Genomics, May 2020). PDGFRA mRNA and Pdgfr-alpha expression have been reported in 85% (79 /93) and 83% (82/99) of colorectal cancer samples analyzed in two separate studies [444, 348].

Role in disease: PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies, leading authors to consider the Pdgfrs as oncoproteins [107]. Both autocrine and paracrine activation of PDGF signaling have been implicated in numerous tumor types [11]. One study reported that Pdgfr-alpha expression correlated with tumor stage and lymph node metastasis in colorectal cancer cases [444].

Diagnostic significance: Unknown.

Variants of potential clinical significance (6)

Prognostic significance: Unknown.

Drug sensitivity: Several tyrosine kinase inhibitors that target the Pdgfrs, as well as other kinases, have received agency approval in various indications. These agents, including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, ponatinib, regorafenib, pazopanib, and lenvatinib, are currently in clinical trials for patients with multiple solid tumor types [69]. Avapritinib has been FDA-approved for the treatment of GIST patients harboring PDGFR mutations in exon 18 [amino acids 814-854 (Integrative Genomics Viewer, v.2.8)]. In addition, olaratumab, a monoclonal antibody targeting Pdgfr-alpha, has been demonstrated to have anti-tumor effects in mouse xenografts derived from multiple cancer types [236, 404]. Regorafenib has been FDA-approved for the treatment of metastatic colorectal carcinoma (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and with an anti-EGFR therapy if wild-type for KRAS [127].

Drug resistance: Secondary resistance to imatinib occurs in most tumors eventually, and can be attributed, for the most part, to the gain of a second KIT or PDGFRA mutation in the same allele as the primary mutation [440, 207, 238].

Approved Drugs: Regorafenib.

Phase 3: Regorafenib has been approved to treat patients with metastatic colorectal cancer based on the results of a trial (Study 14387) of 760 previously treated metastatic colorectal cancer patients; the study reported a significant increase in overall survival (6.4 months versus 5.0 months) and progression-free survival (1.9 months versus 1.7 months) in patients treated with regorafenib as compared with placebo [127]. A Phase 3 study of regorafenib versus placebo in 204 previously treated metastatic colorectal cancer patients of Asian origin reported a median overall survival of 8.8 months in the regorafenib arm (n=136) and 6.3 months in the placebo arm (n=68); adverse events were more frequently reported in the regorafenib arm compared to the placebo arm (97% vs. 46%) [218]. A Phase 3 clinical trial of 768 metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan (FOLFIRI), in combination with sunitinib, did not show significant clinical benefit; sunitinib in combination with FOLFIRI also showed a poor safety profile [46]. A Phase 3 trial (LUME-Colon 1) of nintedanib or placebo plus best supportive care in 768 patients with metastatic colorectal cancer reported median progression-free survival of 1.5 and 1.4 months, and median overall survival of 6.4 and 6.0 months, respectively. Nintedanib was reported to be well tolerated [426].

Phase 2: A Phase 2 study of oxaliplatin, leucovorin, and fluorouracil in combination with sorafenib or placebo in metastatic colorectal cancer reported no benefit in terms of progression-free survival with the addition of sorafenib [391]. A Phase 2 study of lenvatinib in 30 metastatic colorectal carcinoma patients refractory to standard chemotherapy has reported response rate of 6.7%, all partial responses, and disease control rate of 70.0% with median PFS of 3.6 months. A Phase 2 trial of dasatinib in 19 previously treated metastatic colorectal cancer patients was terminated due to lack of efficacy, with no objective responses, stable disease for 7.3 months in one patient, a progression-free survival (PFS) rate at four months of 5.3%, and a median PFS and overall survival of 1.6 and 5.1 months, respectively [355]. A Phase 1b/2 study of dasatinib with FOLFOX or cetuximab in 77 patients with previously treated KRAS codon 12/13 wild-type or mutant metastatic CRC, respectively, has reported response rates of 13% (3/24) and 0/23 in KRAS wild-type and mutant cohorts, respectively and a median progression-free survival of 2.3 months in both the KRAS wild-type and mutant cohorts [292]. A Phase 1/2 study examining imatinib in combination with capecitabine, oxaliplatin, and bevacizumab in 49 patients with CRC reported that 76% of patients were progression-free for at least six months [145].

Phase 1: A Phase 1 study of pazopanib plus gemcitabine in 22 patients with advanced solid tumors reported that the combination was well tolerated; in this study, a partial response was observed in a melanoma patient and stable disease for at least 12 treatment cycles was observed in three patients (one each with cholangiocarcinoma, melanoma, and colorectal cancer) [308]. A Phase 1 study of colorectal cancer patients treated with pazopanib in combination with either FOLFOX6 (20 patients) or CapeOx (21 patients) reported an overall response rate of 40% and 38% with these therapy combinations, respectively [36]. A Phase 1 study of olaratumab in patients with advanced solid tumors reported stable disease (per radiographical review) in 43.8% (7/16) of cases; treatment was described as well-tolerated overall [83]. A Phase 1 study of olaratumab in patients with advanced solid tumors reported stable disease (SD, per RECIST) in 63.2% (12/19) of cases, with median SD duration of 3.9 months; drug-related grade 3 alkaline phosphatase events were noted in one patient, and grade 3 deep vein thromboses were reported in 10.5% (2/19) cases as well [55]. A Phase 1 study of lenvatinib in combination with capecitabine and radiation in 20 patients with locally advanced rectal adenocarcinoma has reported a pathological complete response in 29.4% (5/17) and downstaging in 71% (12 /17) of evaluable patients. No grade 4 adverse events were observed. Several Phase 1 studies have examined imatinib in combination with chemotherapy in colorectal cancer, and have reported efficacy; one study reported that 76% of patients (n=49) were progression-free for at least six months [259, 145, 178].

Preclinical: A preclinical study in a mouse xenograft model of colon cancer reported that nilotinib treatment led to decreased stromal reaction in the colon; a synergistic anti-tumor response was seen at the primary and

Variants of potential clinical significance (6)

metastatic tumor sites upon co-treatment with everolimus [471]. Preclinical studies have reported that ponatinib treatment reduced proliferation, growth, and migration in cell and mouse xenograft models of colorectal cancer [399, 8]. In addition, ponatinib treatment has been reported to result in inhibition of tumor growth in one of two colorectal carcinoma cell models without RET fusions. The effects of ponatinib were significantly enhanced in two colorectal carcinoma cell models harboring RET fusions [124].

PIK3CA amplification

Gene: PIK3CA
Amino Acid: amplification
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
6 Trials

Biomarker summary: PIK3CA-amplification is an activating alteration.

Clinical relevance: PIK3CA encodes the protein p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival [344, 95]. Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [161, 253]. In addition, the p110-alpha inhibitor alpelisib has been approved by the FDA for the treatment of postmenopausal women, and men, with PIK3CA-mutated, hormone receptor-positive, Her2-negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy [12].

Disease summary: Upregulation of PIK3CA mRNA has been reported in colorectal carcinoma cases, as compared with normal mucosa, and overexpression of p110-alpha has also been detected by IHC in 59% (235 /398) of colorectal cancer samples, as compared with normal mucosa [164, 68]. Increased expression of p110-alpha has been correlated with tumor size and stage, as well as with regional lymph node metastases in colorectal cancer [68]. PIK3CA expression has also been implicated in tumor growth, migration, and invasion in preclinical models of colorectal cancer [455].

Molecular function: Amplification of PIK3CA has been correlated with PIK3CA mRNA and p110-alpha expression in several tumor types, and with activation of the PI3K/Akt pathway and tumorigenesis [225, 313, 13, 356, 467].

Incidence: Putative high-level amplification of PIK3CA has not been reported in any Colorectal adenocarcinoma (0/592) cases (Colorectal Adenocarcinoma (TCGA, PanCancer Atlas), cBioPortal for Cancer Genomics, May 2020). PIK3CA amplification in colorectal carcinoma patient samples has been variably reported in the scientific literature with incidences ranging from 4-77% [164, 58, 466]. Upregulation of PIK3CA mRNA has been reported in colorectal carcinoma cases, as compared with normal mucosa, and overexpression of p110-alpha has also been detected by IHC in 59% (235/398) of colorectal cancer samples, as compared with normal mucosa [164, 68].

Role in disease: PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt [460, 160]. Increased expression of p110-alpha has been correlated with tumor size and stage, as well as with regional lymph node metastases in colorectal cancer [68]. PIK3CA expression has also been implicated in migration, invasion, and tumor growth in preclinical models of colorectal cancer [455].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [161, 253]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy [161, 235, 244, 146, 270]. Other agents that target mTOR, including dual mTORC1 /mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development [80, 114, 192]. In addition, the p110-alpha inhibitor alpelisib has been approved by the FDA for the treatment of postmenopausal women, and men, with PIK3CA-mutated, hormone receptor-positive, Her2-negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy [12]. Studies have reported that patients with PIK3CA-mutant colorectal cancer are more likely to benefit from aspirin therapy than patients with wild-type PIK3CA [477, 287, 223, 84]. However, another study proposes that HLA antigen status may be more important than PIK3CA mutation status in predicting response to aspirin in colorectal cancer patients [324].

Drug resistance: A meta-analysis of 13 studies, including 576 patients, reports that PIK3CA exon 20 mutations (amino acids 929-979), but not exon 9 mutations (amino acids 469-513), may predict a poor response to cetuximab or panitumumab in KRAS wild-type colorectal cancer patients [250].

Approved Drugs: None.

Variants of potential clinical significance (6)

Phase 3: None.

Phase 2: A Phase 2 trial of MK-2206 and selumetinib treatment in 21 colorectal cancer patients, including KRAS wild-type and KRAS-mutant cases, has reported no objective responses. Furthermore, no tumors showed at least a 70% reduction of both p-ERK and p-Akt expression levels after treatment [81]. In a Phase 2 clinical trial of buparlisib within a cohort of 18 colorectal cancer patients, two patients had stable disease at eight weeks; adverse events were reported, including in three patients who discontinued treatment due to adverse events. At 16 weeks, none of the 13 evaluable patients met criteria for clinical benefit, suggesting a lack of clinical activity of single agent buparlisib. A Phase 2 basket of buparlisib monotherapy in 146 patients with solid tumors harboring PIK3CA, PIK3R1, or PTEN alterations, including 18 patients with colorectal carcinoma, has reported a clinical benefit rate of 15.1%, including one confirmed partial response and 21 stable diseases, while an additional patient achieved an unconfirmed complete response; no colorectal carcinoma patients achieved a clinical benefit [363, 303].

Phase 1: A Phase 1 trial of capivasertib (AZD5363) in 90 solid tumor patients has reported stable disease for more than 6 and 12 weeks in 30% (27/90) and 7% (6/90) of patients, respectively, and one partial response in a cervical cancer patient with a PIK3CA mutation. In an expansion cohort of patients with PIK3CA mutations, confirmed RECIST responses were observed in 1/28 and 8% (2/26) of breast and gynecologic cancer patients, respectively, resulting in termination of further enrollment [19]. A Phase 1 study of capivasertib (AZD5363) in 41 Japanese solid tumor patients has reported confirmed partial responses in 5% (2/37) of evaluable patients, both with the AKT1 E17K mutation, and stable disease in 27% (10/37) of patients. Grade 3 or higher treatment-related adverse events were observed in 58.5% of patients [398]. A Phase 1b study of encorafenib and cetuximab with or without alpelisib in BRAF-mutated colorectal carcinoma patients has reported median progression-free survival (PFS) of 4.2 months, an overall response rate (ORR) of 17.9% (5/28), and a disease control rate (DCR) of 92.8% (26/28) for patients who received all three drugs as compared with median PFS of 3.7 months, an ORR of 19.2% (5/26), and a DCR of 76.9% (20/26) for those patients who only received encorafenib and cetuximab [479]. A Phase 1 study of copanlisib in 48 patients with advanced solid tumors reported one complete response in an endometrial carcinoma patient with PIK3CA activation and PTEN loss, as well as two partial responses in metastatic breast cancer patients [296].

Preclinical: Combination treatment with PI3K inhibitor buparlisib and MEK inhibitor mirdametinib (PD0325901) was reported to induce tumor regression in a mouse model of PIK3CA wild-type, KRAS-mutant colorectal cancer [332]. Capivasertib (AZD5363) has been reported to inhibit viability of patient-derived colon cancer cells as a single agent and in combination with cetuximab in one study [183].

TP53 P278S

Gene: TP53
Exon: 8
Nucleotide:
NM_000546.6:
g.7577106G>A
c.832C>T
Amino Acid: p.P278S
Allelic Fraction: 20.0% (of 201 reads)
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
3 Sensitive
1 Resistance
3 Trials

Biomarker summary: TP53-P278S is an inactivating mutation.

Clinical relevance: TP53 is a tumor suppressor that encodes the p53 protein; alterations in TP53 may result in a loss of p53 function, yet an increase in the expression and stability of the mutant p53 protein in the nucleus, sometimes leading to oncogenic effects, including genomic instability and excessive cell proliferation [214, 439, 190, 174, 147, 282]. At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines [351, 429, 341]. Tumors with TP53 mutations may be sensitive to the Wee1 inhibitor adavosertib (MK-1775), and clinical trials are currently underway for patients with solid tumors and hematologic malignancies [142, 37]. Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers [432, 221, 172, 408, 170].

Disease summary: TP53 mutations have been associated with distal tumor location, left-sided disease, microsatellite stability (MSS), non-mucinous histology, and high levels of chromosomal instability in studies of colorectal carcinoma (CRC) [396, 206, 224, 480, 383, 179, 414]. Additionally, p53 expression in CRC has been positively correlated with distal tumor location, advanced TNM stage, and high Ki67 expression [450, 258, 256, 152, 45, 437, 2].

Molecular function: TP53 P278S is a missense alteration located within the DNA-binding domain (DBD) of the p53 protein [165]. DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes [174]. TP53 P278S has been characterized as inactivating and oncogenic in cell line assays, and dominant-negative in a heterozygous mouse model harboring the analogous mutation; additional research is needed to confirm an oncogenic role for this alteration [428, 478].

Incidence: TP53 mutations have been reported in 45% (6195/13800) of Colorectal adenocarcinoma samples analyzed in COSMIC (May 2020). TP53 mutations have been reported in 56-80% of Colorectal adenocarcinoma samples (cBioPortal for Cancer Genomics, May 2020). Literature studies have reported TP53 mutations in 21-72% of CRC samples [179, 239, 200, 364, 378, 269, 49, 247, 376, 48].

Variants of potential clinical significance (6)

Role in disease: Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [39]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [248, 375, 345]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [439, 190, 174, 147, 282]. TP53 mutations have been associated with distal tumor location, left-sided disease, microsatellite stability (MSS), non-mucinous histology, and high levels of chromosomal instability in studies of colorectal carcinoma (CRC) [396, 206, 224, 480, 383, 179, 414]. Additionally, p53 expression in CRC has been positively correlated with distal tumor location, advanced TNM stage, and high Ki67 expression [450, 258, 256, 152, 45, 437, 2].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines [351, 429, 341]. Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function [242, 142, 37]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors [432, 221, 172, 408, 130, 252].

Drug resistance: Mutations in TP53 may increase resistance to ionizing radiation therapy [93, 263].

Approved Drugs: None.

Phase 3: None.

Phase 2: A Phase 2 study of alisertib in 139 pediatric patients with solid tumors or leukemia has reported complete and partial responses in two and three patients, respectively [266].

Phase 1: A Phase 1 study of ENMD-2076 in patients with advanced cancer reported stable disease of 12 weeks or longer in 26% (5/19) of colorectal cancer patients. Therapy was reported to be well-tolerated overall, with hypertension, nausea/vomiting, and fatigue being the most common adverse events [79]. A Phase 1 trial of adavosertib (AZD1775, MK-1775) in 21 evaluable patients with refractory solid tumors, including seven patients with documented BRCA1/2 mutations, reported confirmed partial responses in one head and neck cancer and one ovarian cancer patient, both harboring BRCA1 mutations; however, no responses were seen in any of five patients with confirmed TP53 mutations [82]. A Phase 1 trial of adavosertib alone or in combination with chemotherapy in patients with refractory solid tumors has reported confirmed or unconfirmed partial responses in 10% (17/176) of patients overall, including in patients with ovarian cancer, melanoma, breast cancer, head and neck cancer, colorectal cancer, and cutaneous squamous cell carcinoma. In patients with archived tumor tissue evaluable for sequence analysis, partial responses were reported in 21% (4/19) and 12% (4/33) of TP53 mutant and TP53 wild-type cases, respectively. Stable disease was reported in 53% (94/176) of patients overall [213]. A Phase 1 study of adavosertib (AZD1775) in combination with irinotecan in 27 evaluable pediatric patients with relapsed/refractory solid tumors or central nervous system tumors has reported a confirmed partial response in an Ewing sarcoma patient and prolonged stable disease in two patients, one each with ependymoma and neuroblastoma. Grade 3 dehydration, which was experienced by two patients, was reported as a dose-limiting toxicity [62]. A Phase 1 study of alisertib, an Aurora A kinase inhibitor, in patients with solid tumors noted a durable response for longer than one year in one patient and stable disease for at least three months in 23% (20/87) of patients [78]. A Phase 1 study of alisertib in combination with docetaxel in 41 adults with advanced solid tumors has reported partial response in 29% (8 /28) of efficacy-evaluable patients, including one complete response in a bladder cancer patient, one partial response in an angiosarcoma patient, and six partial responses in castration-resistant prostate cancer patients [125]. A Phase 1 trial of SGT-53 in 11 patients with refractory cancer reported that the gene therapy complex was well tolerated with stable disease achieved in seven patients at six weeks and a median survival of 340 days; in addition, one tumor which was previously classified as inoperable was able to be resected [354]. A Phase 1 trial of SGT-53 in combination with docetaxel in 14 patients with advanced cancer has reported three partial responses and two stable diseases per RECIST [305].

Preclinical: In preclinical experiments, the Wee1 tyrosine kinase inhibitor adavosertib appeared to sensitize p53-deficient tumor cells to chemotherapeutic agents and to radiation; in particular, in several p53-deficient human colon cancer cell lines, adavosertib has been reported to enhance the cell growth inhibition of 5-fluorouracil or capecitabine [465, 37, 142, 320, 441]. Alisertib has been reported to inhibit proliferation of

Variants of potential clinical significance (6)

colorectal carcinoma cell lines and inhibit tumor growth in 33% (7/21) of colorectal patient-derived xenograft models utilized in one study [306]. A preclinical study reported that treatment of breast cancer, non-small cell lung cancer, and glioblastoma mouse models with SGT-53 resulted in sensitivity to anti-PD1 antibodies; the combination therapy resulted in greater activation of tumor infiltrating lymphocytes and synergistic tumor growth inhibition as compared with either treatment alone [186].

Variants of biological significance (2)

MPL R102P

Gene: MPL
Exon: 3
Nucleotide: NM_005373.3: g.43804305G>C c.305G>C
Amino Acid: p.R102P
Allelic Fraction: 50.0% (of 343 reads)
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: MPL-R102P exhibits altered function compared to wild-type.

Clinical relevance: MPL encodes the thrombopoietin receptor (TPO-R) protein [88, 271, 18]. Activating MPL mutations have been associated with increased Jak/Stat signaling and may predict sensitivity to Jak inhibitors [304, 196, 281, 188]. The FDA-approved Jak inhibitor ruxolitinib and other agents targeting the Jak/Stat pathway are in clinical trials in solid tumors and hematologic malignancies [397, 74, 430, 431, 132, 388]. As MPL R102P may have differential effects in vivo depending on whether it occurs as a heterozygous or homozygous alteration, the relevance of any therapeutic approaches is unknown [24, 412, 481].

Disease summary: MPL mRNA has been reported to be downregulated in colorectal carcinoma samples as compared with matched normal tissue in one study of 245 colorectal carcinoma cases [362].

Molecular function: MPL R102P is a missense alteration that occurs within the extracellular domain of the TPO-R protein (UniProt), which contains two cytokine receptor homology modules that have been reported to be important for mediating signaling and cellular proliferation [340]. MPL R102P has been reported as a germline mutation in patients with congenital amegakaryocytic thrombocytopenia and has been characterized as an inactivating mutation, defective in downstream activation of Stat3 and Akt [412, 481]. However, one study has identified MPL R102P as a heterozygous mutation in patients with hereditary thrombocytosis and high levels of TPO were reported in the serum of patients harboring this heterozygous alteration [24]. Therefore, MPL R102P may have differential effects in vivo depending on whether it occurs as a heterozygous or homozygous alteration.

Incidence: MPL mutations have been reported in 1.4% (37/2631) of Colorectal adenocarcinoma samples analyzed in COSMIC (May 2020). MPL mutations have been reported in 0.0-2.4% of Colorectal adenocarcinoma samples (cBioPortal for Cancer Genomics, May 2020). One study has reported MPL mutations in 1/91 Brazilian colorectal cancer cases, specifically in a MSI-positive tumor from the proximal colon [86].

Role in disease: The MPL gene product, TPO-R, is a cytokine receptor that promotes megakaryocyte differentiation through the Jak/Stat and MAPK/ERK signaling pathways [88, 271, 18].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are no approved therapies that directly target MPL mutations in cancer. However, activating MPL mutations have been associated with increased Jak/Stat signaling and may predict sensitivity to Jak inhibitors [304, 196, 281, 188]. The FDA-approved Jak inhibitor ruxolitinib and other agents targeting the Jak/Stat pathway are in clinical trials in solid tumors and hematologic malignancies [397, 74, 430, 431, 132, 388].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

SHQ1 D277fs*27

Gene: SHQ1

Biomarker summary: The effect of SHQ1-D277fs*27 has not been determined by N-of-One.

Variants of biological significance (2)

Exon: 7
Nucleotide: NM_018130.3: g.72866432_72866435delATCA c.828_831delTGAT
Amino Acid: p.D277fs*27
Allelic Fraction: 44.0% (of 237 reads)
Classification: Tier 3
Assessment: Pathogenic

Clinical relevance: SHQ1 encodes protein SHQ1 homolog, or Shq1, an assembly factor required for biogenesis and processing of ribonucleoproteins [128]. Loss of the chromosomal region encompassing SHQ1 and reduced SHQ1 mRNA expression, as compared with normal tissue, have been reported in several tumor types and have been observed to promote tumorigenesis in preclinical cancer models [407, 275, 202, 199, 453, 56, 141]. There are currently no therapeutic approaches targeting SHQ1 alterations. As SHQ1-D277fs*27 has not been analyzed by N-of-One, the relevance of any therapeutic approaches is uncertain.

Disease summary: Please note: This gene has not been researched in the context of this specific cancer type by N-of-One.

Molecular function: SHQ1-D277fs*27 has not been analyzed by N-of-One; therefore its effect on protein function cannot be described.

Incidence: SHQ1 mutations have been reported in less than 1% (22/2356) of Colorectal adenocarcinoma samples analyzed in COSMIC (May 2020). SHQ1 mutations have been reported in 0.0-1.9% of Colorectal adenocarcinoma samples (cBioPortal for Cancer Genomics, May 2020).

Role in disease: Loss of the chromosomal region encompassing SHQ1 and reduced SHQ1 mRNA expression, as compared with normal tissue, have been reported in several tumor types and have been observed to promote tumorigenesis in preclinical cancer models [407, 275, 202, 199, 453, 56, 141]. Please note: This gene has not been researched in the context of this specific cancer type by N-of-One.

Diagnostic significance: Please note: This gene has not been researched in the context of this specific cancer type by N-of-One.

Prognostic significance: Please note: This gene has not been researched in the context of this specific cancer type by N-of-One.

Drug sensitivity: As the functional consequences of SHQ1-D277fs*27 have not been analyzed by N-of-One, the relevance of any available therapies and clinical trials targeting this alteration is uncertain. Please note: This gene has not been researched in the context of this specific cancer type by N-of-One.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

Variants of uncertain significance (9)

Gene	Variant	Allelic fraction	Classification
CYLD	c.2465C>T p.T822I	45.0% (of 186 reads)	Tier 3, Uncertain Significance
FANCA	c.3698C>T p.A1233V	44.0% (of 158 reads)	Tier 3, Uncertain Significance
PAX7	c.1187C>T p.P396L	57.0% (of 176 reads)	Tier 3, Uncertain Significance
RAD21	c.1711C>T p.L571F	39.0% (of 210 reads)	Tier 3, Uncertain Significance
SLIT2	c.4025G>A p.S1342N	50.0% (of 294 reads)	Tier 3, Uncertain Significance
SLX4	c.1616C>T p.A539V	55.0% (of 244 reads)	Tier 3, Uncertain Significance
SOX2	c.859G>C p.A287P	33.0% (of 95 reads)	Tier 3, Uncertain Significance
SUFU	c.1296+74C>T	47.0% (of 232 reads)	Tier 3, Uncertain Significance
TCF3	c.1085G>A p.G362D	42.0% (of 140 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested

Methods and limitations

Please refer to the Project Summary report from Genomic Services for detailed methods.

QIAGEN's variant analysis and interpretation service is intended for research labs analyzing human genetics data and is not intended to be used for diagnostic purposes. The content contained herein ("Content") is a publication of QIAGEN. QIAGEN does not provide medical services, nor is any QIAGEN employee engaged in the practice of medicine for or on behalf of QIAGEN. Some tests, drugs and biomarkers identified in this report may not be approved by the FDA for a particular use or validated for that use. The Content is compiled from sources believed to be reliable. Extensive efforts have been made to make the Content as accurate and as up-to-date as possible. The Content may contain typographical errors and omissions. The Content is for research use only. The following underlying databases, date reference sets and tools were used: QIAGEN Clinical Insight-Interpret (7.0.20201130), Ingenuity Knowledge Base (B-release), CADD (v1.6), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2020-04-06), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2020-11-17 10:02:34.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (B-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Nov 20 02:39), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 33), CentoMD (5.3), OMIM (July 06, 2020), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2020-09-15), DGV (2016-05-15), COSMIC (v92), HGMD (2020.3), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 153, GRCh38 153), SIFT4G (2016-02-23)

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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