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Consulting physician		Patient		Sample	
Provider	General Hospital	Age	64	Accession Number	TSO500_CRC_MSI_TMB
Physician	Dr. E Schmidt	Gender	Male	Collection site	Colon
Pathologist	Dr. R Braun	Diagnosis	Colorectal Carcinoma	Type	Biopsy
Report Date	08.04.2021	Stage	IV	Collection date	08.04.2021

Panel Analysis: TSO500

The TruSight Oncology 500 panel enables in-house, pan-cancer comprehensive genomic profiling (CGP) for solid tumors from either blood or tissue biopsy samples; the panel is designed to identify relevant biomarkers in guidelines and trials, including the immuno-oncology markers TMB and MSI.

Analysis results: Positive

2 Biomarkers	Approved treatments	Other findings
Tumor Mutation Burden: TMB-high (37.2 Mutations/Megabase)	Pembrolizumab	Other Indications: ipilimumab /nivolumab, nivolumab Trials: 1 Phase 2
Microsatellite Status: MSI-high	Durvalumab Ipilimumab/nivolumab Nivolumab Pembrolizumab	Trials: 3 Phase 2 2 Phase 1

3 Variants of potential clinical significance, Tier 2	Approved treatments	Other findings
ARID1A: p.H688fs*129, Likely Pathogenic	-	-
MSH2: p.N538fs*5, Likely Pathogenic	-	-
MSH2: p.N835fs*4, Pathogenic	-	-

6 Variants of uncertain significance, Tier 3

Interactions

None

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

Approval

Electronically signed on: 08.04.2021 by Dr. Schmidt

Report content

GUIDELINES

The ESMO Clinical Practice Guidelines suggest testing for microsatellite instability (MSI) in all newly diagnosed patients with colon cancer and note that the presence of MSI may predict sensitivity to immune check point inhibitors; the Guidelines additionally note that stage 2 MSI-high colorectal carcinoma patients may have a good prognosis and may not benefit from adjuvant 5FU therapy [PMID:32702383, PMID:27380959].

TREATMENT OPTIONS

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; for treating adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with 2 cycles of platinum-doublet chemotherapy; and for treating patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment; nivolumab, in combination with ipilimumab, is 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; for treating adult patients with unresectable malignant pleural mesothelioma, as first-line treatment; 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; and for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib.

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

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; for treating adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with 2 cycles of platinum-doublet chemotherapy; and for treating patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment; nivolumab, in combination with ipilimumab, is 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; for treating adult patients with unresectable malignant pleural mesothelioma, as first-line treatment; 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; and for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib.

Sensitive
Biomarkers: Tumor Mutation Burden: TMB-high, Tier 1A
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; for treating adult patients with 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 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); intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab; advanced renal cell carcinoma who have received prior antiangiogenic therapy; 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; 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; and unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based 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; unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab; for treating patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib; 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; and for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.

Sensitive
Biomarkers: Tumor Mutation Burden: TMB-high, Tier 1A
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; for treating adult patients with 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 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); intermediate or poor risk advanced renal cell carcinoma, as

Therapies with potential clinical benefit (6)

a first-line treatment in combination with ipilimumab; advanced renal cell carcinoma who have received prior antiangiogenic therapy; 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; 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; and unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based 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; unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab; for treating patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib; 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; and for treating patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.

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

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.

Therapies with potential clinical benefit (6)

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

DURVALUMAB

Durvalumab, a programmed death-ligand 1 (PD-L1) blocking antibody, is FDA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; for treating patients with unresectable, stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy; and, in combination with etoposide and either carboplatin or cisplatin, as first-line treatment for adult patients with extensive-stage small cell lung cancer (ES-SCLC); durvalumab is EMA-approved for treating adult patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

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

AVAILABLE CLINICAL TRIALS

Phase 2 clinical trials (3)

IPILIMUMAB, ATEZOLIZUMAB, NIVOLUMAB

The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy
NCT04591431

Qualifying variants			Contact
Biomarker	Classification	Score	Silvia Violetti; silvia.violetti@clinicaltrialsfmp.it;
TMB-high	Tier 1A Pathogenic	37.2 Mutations/Megabase	+390683977939;
MSI-high	Tier 1A Pathogenic	-	

ATEZOLIZUMAB

A Phase II Study to Assess the Efficacy of the Anti-PD-L1 Antibody Atezolizumab (MPDL3280A) Administered With Stereotactic Ablative Radiotherapy (SABR) in Patients With Metastatic Tumours
NCT02992912

Qualifying variant			Contact
Biomarker	Classification	Score	Eric DEUTSCH, MD, PhD; eric.deutsch@gustaveroussy.fr;
MSI-high	Tier 1A Pathogenic	-	0142114211 +33;

CETUXIMAB, BEVACIZUMAB, AFLIBERCEPT, AVELUMAB, 5-FLUOROURACIL/IRINOTECAN/LEUCOVORIN, 5-FLUOROURACIL/LEUCOVORIN/OXALIPLATIN, PANITUMUMAB

Multicenter Randomized Phase II Study Comparing the Effectiveness and Tolerance of Avelumab Versus Standard 2nd Line Treatment Chemotherapy in Patients With Colorectal Metastatic Cancer With Microsatellite Instability (MSI)
NCT03186326

Qualifying variant			Contact
Biomarker	Classification	Score	Jérémie BEZ; jeremie.bez@u-bourgogne.fr;
MSI-high	Tier 1A Pathogenic	-	+33 (3)80 39 34 83;

Phase 1 clinical trials (2)

IPILIMUMAB, PEXASTIMOGENE DEVACIREPVEC

A Phase I Dose Escalation Trial Evaluating the Impact of an in Situ Immunization Strategy With Intra-Tumoral Injections of Pexa-Vec in Combination With Ipilimumab in Metastatic / Advanced Solid Tumors With Injectable Lesions.
NCT02977156

Qualifying variant			Contact
Biomarker	Classification	Score	Aurélien MARABELLE, MD, PhD; aurelien.marabelle@gustaveroussy.fr;
MSI-high	Tier 1A Pathogenic	-	

MP0310

A First-In-Human, Single-Arm, Multi-Center, Open-Label, Repeated-Dose, Dose-Escalation Study of MP0310 in Patients With Advanced Solid Tumors
NCT04049903

Qualifying variant			Contact
Biomarker	Classification	Score	Medical Director, MPAG; info@molecularpartners.com;
MSI-high	Tier 1A Pathogenic	-	+41 44 755 7700;

VARIANT DETAILS

Biomarkers (2)

Tumor Mutation Burden: TMB-high (37.2 Mutations/Megabase)

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

Treatment options
3 Sensitive
1 Trial

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) [106, 6, 153, 58]. 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 [72, 58, 17, 143]. 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 [141, 20, 54, 140, 52, 71, 197, 144, 80, 60, 148].

Disease summary: High mutational burden has been associated with microsatellite instability (MSI) and mismatch-repair deficiency (MMR-D) in studies of colorectal carcinoma [165, 105, 97, 21, 49, 98].

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 [21, 43]. In a study of 246 left-sided and 56 right-sided colorectal tumors in young adults and adolescents, TMB-high status was found more often in right-sided tumors, regardless of MSI status [146].

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 [106, 6]. 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) [58, 153, 143]. High mutational burden has been associated with microsatellite instability (MSI) and mismatch-repair deficiency (MMR-D) in studies of colorectal carcinoma [165, 105, 97, 21, 49, 98].

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 [72, 58, 17, 143]. 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 [148].

Drug resistance: None.

Approved Drugs: None.

Phase 3: The second interim analysis of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 patients with MSI-high or deficient MMR metastatic colorectal carcinoma has reported a progression-free survival of 16.5 and 8.2 months, a confirmed overall response rate of 43.8% and 33.1%, an estimated restricted mean survival of 13.7 and 10.8 months, and grade 3-5 serious adverse events in 22% and 66% of patients treated with pembrolizumab or chemotherapy, respectively. Ongoing responses at 24 months were observed in 83% and 35% of patients treated with pembrolizumab or chemotherapy, respectively [8]. 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 [45].

Phase 2: The Phase 2 KEYNOTE-158 study of pembrolizumab in advanced solid tumor patients has reported an overall objective response in 29% (30/102) of patients with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase [115]. 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 [198]. 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

Biomarkers (2)

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 [129]. A Phase 2 study of nivolumab in combination with trifluridine/tipiracil in 18 patients with MSS colorectal carcinoma has reported 13 grade 3 or higher adverse events, no tumor responses, stable disease in eight and ten patients, and a median progression-free survival of 2.2 and 2.8 months per immune-related response criteria (irRC) and RECIST, respectively [131]. 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. 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 1.9 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 [28]. A Phase 2 study of durvalumab and trametinib in 29 microsatellite stable metastatic colorectal cancer patients has reported objective response in 3.4% and stable disease in 24% of patients. No grade 4 treatment-related adverse events were observed. 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%. The Phase 2 CAVE study of avelumab and cetuximab in RAS wild-type metastatic colorectal carcinoma patients with response to first-line chemotherapy in combination with anti-Egfr therapy has reported complete response in 1.5%, partial response in 4.6%, and stable disease in 49.2% of 65 evaluable patients. Median progression-free and overall survival were 3.6 months and 13.1 months, respectively, and grade 3 adverse events were observed in 22% (16/77) of patients. A Phase 2 study of avelumab monotherapy in 33 metastatic or unresectable colorectal carcinoma patients with dMMR/MSI-H or POLE mutations has reported objective response rate of 24.2% and median progression-free survival and overall survival of 3.9 and 13.2 months, respectively [88]. A Phase 2 study of short-course radiation followed by mFOLFOX6 with avelumab in 13 patients with locally advanced rectal cancer has reported pathologic complete response (pCR) in 3/12 and near pCR in 3/12 evaluable patients. No grade 4 serious adverse events were observed [156].

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
4 Sensitive
5 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 [86, 5, 72, 174, 109]. Thus, checkpoint inhibitors, several of which have received agency approval for certain indications, may be clinically relevant for tumors exhibiting MSI [122, 176, 130, 172, 97, 187]. 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 by the FDA and EMA for colorectal carcinoma patients with MSI-H or dMMR [102, 97].

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 [164, 173, 27, 53, 9]. Adjuvant 5-FU may not benefit colorectal cancer patients with stage II/III MSI-H tumors when given as monotherapy [139, 150, 171].

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 [12, 179].

Incidence: MSI has been reported in 3-24% of colorectal carcinoma samples and has been observed in both inherited and sporadic forms of the disease [59, 169, 110, 30, 164, 126, 178, 137, 70, 170, 53].

Biomarkers (2)

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) [111, 34, 70]. 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 [86, 5, 72, 174]. 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 [164, 9, 173, 27, 53]. 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 [92, 181, 147, 99, 123].

Diagnostic significance: Unknown.

Prognostic significance: Several studies have reported MSI-high status to be associated with better prognosis in colorectal carcinoma patients compared with patients lacking MSI-high [183, 66, 188, 136].

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 [109, 97, 72]. Checkpoint inhibitors are currently in clinical development, several of which have received agency approval for certain indications [122, 187]. 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 [107].

Drug resistance: Adjuvant 5-FU may not benefit colorectal cancer patients with stage II/III MSI-H tumors when given as monotherapy [139, 150, 171]. 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 [139, 150, 171, 68].

Approved Drugs: Pembrolizumab.

Phase 3: The second interim analysis of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 patients with MSI-high or deficient MMR metastatic colorectal carcinoma has reported a progression-free survival of 16.5 and 8.2 months, a confirmed overall response rate of 43.8% and 33.1%, an estimated restricted mean survival of 13.7 and 10.8 months, and grade 3-5 serious adverse events in 22% and 66% of patients treated with pembrolizumab or chemotherapy, respectively. Ongoing responses at 24 months were observed in 83% and 35% of patients treated with pembrolizumab or chemotherapy, respectively [8]. 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 [45].

Phase 2: 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 [116, 102, 97]. 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. 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 [198]. 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 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. The Phase 2 GERCOR NIPICOL study of nivolumab plus ipilimumab in 57 pretreated patients with MSI-H/dMMR metastatic colorectal cancer has reported 12-week disease control rate of 86.0% and 87.7%, and 12-month progression-free survival rate of 72.9% and 76.5%, according to RECIST 1.1 and iRECIST criteria, respectively. Overall response rate was 59.7% [33]. The Phase 2 NICHE study of neoadjuvant ipilimumab and nivolumab in early-stage colon cancer patients has reported pathological response in 100% (20/20) of patients with MMR-deficient tumors and in 27% (4/15) of patients with MMR-proficient tumors [25]. A Phase 2 study of nivolumab in 74 dMMR or MSI-H CRC patients has reported

Biomarkers (2)

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 [129]. A Phase 2 study of nivolumab in combination with trifluridine/tipiracil in 18 patients with MSS colorectal carcinoma has reported 13 grade 3 or higher adverse events, no tumor responses, stable disease in eight and ten patients, and a median progression-free survival of 2.2 and 2.8 months per immune-related response criteria (irRC) and RECIST, respectively [131]. 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. 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 1.9 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 [28]. A Phase 2 study of durvalumab and trametinib in 29 microsatellite stable metastatic colorectal cancer patients has reported objective response in 3.4% and stable disease in 24% of patients. No grade 4 treatment-related adverse events were observed. 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%. The Phase 2 CAVE study of avelumab and cetuximab in RAS wild-type metastatic colorectal carcinoma patients with response to first-line chemotherapy in combination with anti-Egfr therapy has reported complete response in 1.5%, partial response in 4.6%, and stable disease in 49.2% of 65 evaluable patients. Median progression-free and overall survival were 3.6 months and 13.1 months, respectively, and grade 3 adverse events were observed in 22% (16/77) of patients. A Phase 2 study of avelumab monotherapy in 33 metastatic or unresectable colorectal carcinoma patients with dMMR/MSI-H or POLE mutations has reported objective response rate of 24.2% and median progression-free survival and overall survival of 3.9 and 13.2 months, respectively [88]. A Phase 2 study of short-course radiation followed by mFOLFOX6 with avelumab in 13 patients with locally advanced rectal cancer has reported pathologic complete response (pCR) in 3/12 and near pCR in 3/12 evaluable patients. No grade 4 serious adverse events were observed [156].

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.

Variants of potential clinical significance (3)

ARID1A H688fs*129

Gene: ARID1A
Exon: 5
Nucleotide:
NM_006015.6:
g.27087482_2708748
3insC
c.2060dupC
Amino Acid: p.H688fs*129
Allelic Fraction: 16.0% (of 1147 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Biomarker summary: ARID1A-H688fs*129 is an inactivating mutation.

Clinical relevance: ARID1A encodes Arid1a, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and functional studies have implicated it as a tumor suppressor [190, 82, 67, 81]. There are no approved targeted therapies that directly target ARID1A alterations at this time. However, inactivating ARID1A mutations and loss of Arid1a expression may predict sensitivity to Ezh2 inhibitors [11]. Small molecule inhibitors of Ezh2, such as tazemetostat, are currently under investigation in clinical studies [91, 36]. In addition, ARID1A-deficient preclinical cancer models exhibit sensitivity to Atr, PARP, and BET domain inhibitors and clinical trials are evaluating these agents in patients with loss of Arid1a expression or ARID1A mutations [192, 159, 10, 24].

Disease summary: Loss of Arid1a expression in colorectal carcinoma has been correlated with mismatch repair (MMR) deficiency and poor tumor differentiation [200, 31, 189, 100, 195]. ARID1A bi-allelic deletion has been reported to result in the development of colon adenocarcinoma in mice, however, in a separate study, ARID1A depletion has been observed to reduce cell viability in KRAS-mutant colorectal carcinoma cell lines [119, 154].

Molecular function: This frameshift alteration is expected to effectively truncate the Arid1a protein prior to the ARID domain, resulting in the loss of the entire ARID domain and three of four LXXLL motifs (UniProt), which

Variants of potential clinical significance (3)

are protein-protein interaction motifs and may mediate the binding of Arid1a with nuclear receptors [35]. The ARID domain is required for Arid1a-DNA interactions and promoter occupancy by SWI/SNF chromatin-remodeling complex [26]. ARID1A mutations, which are mostly truncating mutations, have been shown to be correlated with loss of Arid1a protein and predicted to be inactivating [81, 190, 82]. Therefore, this alteration is predicted to lead to a loss of Arid1a function.

Incidence: ARID1A mutations have been reported in 10% (371/3643) of Colorectal carcinoma (CRC) samples analyzed in COSMIC (May 2020). ARID1A mutations have been reported in 9.4-11% of Colorectal carcinoma (CRC) samples (cBioPortal for Cancer Genomics, May 2020). Other studies have reported ARID1A mutations in 6-10% of CRC cases; however, one study of microsatellite-unstable CRC reports ARID1A mutation in 39% of cases [21, 81, 19, 101].

Role in disease: Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma [158, 31, 7]. Loss of Arid1a expression in colorectal carcinoma has been correlated with mismatch repair (MMR) deficiency and poor tumor differentiation [200, 31, 189, 100, 195]. ARID1A bi-allelic deletion has been reported to result in the development of colon adenocarcinoma in mice, however, in a separate study, ARID1A depletion has been observed to reduce cell viability in KRAS-mutant colorectal carcinoma cell lines [119, 154].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors [11]. Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas [94, 91, 36]. In addition, ARID1A-deficient preclinical cancer models exhibit sensitivity to Atr, PARP, and BET domain inhibitors and clinical trials are evaluating these agents in patients with loss of Arid1a expression or ARID1A mutations [192, 159, 10, 24].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: A Phase 2 trial of olaparib in 20 patients with microsatellite stable (MSS) colorectal cancer (CRC) and 13 with CRC with high-level microsatellite instability (MSI) has reported no complete or partial responses, with a median progression-free survival for all patients of 1.84 months; similar median progression-free and overall survival times were noted regardless of MSS or MSI status [103]. A Phase 2 study of veliparib with temozolomide in 75 metastatic colorectal carcinoma patients has reported a disease control rate of 24% with two confirmed partial responses; median progression-free survival was 1.8 months, and median overall survival was 6.6 months, with dose reductions required in some patients due to myelosuppression [133]. A Phase 2 study of FOLFIRI with veliparib or placebo in 130 patients with metastatic colorectal carcinoma reported objective response rates of 56.9% and 61.5%, median progression-free survival of 12 and 11 months, and median overall survival of 25 and 27 months, in the veliparib and placebo arms, respectively [61, 62].

Phase 1: A Phase 1 trial of niraparib in patients with advanced solid tumors has reported partial responses in 2 /4 breast cancer patients with germline BRCA1/2 mutations and in 40% (8/20) of ovarian cancer patients with BRCA1/2 mutations, as well as anti-tumor activity in sporadic high-grade serous ovarian cancer, non-small cell lung cancer, and prostate cancer [149]. A Phase 1 trial of talazoparib in 110 patients with advanced solid tumors, including 71 patients in the expansion cohort, has reported an overall response rate of 22% (16/72), including two and 14 patients with complete and partial responses, respectively, and 16 stable diseases per RECIST in the expansion cohort [204]. A Phase 1 trial of talazoparib combined with irinotecan with or without temozolomide in 41 pediatric patients with recurrent or refractory solid malignancies has reported an overall response rate of 10.3% in the talazoparib combined with irinotecan arm compared with 25% in the talazoparib combined with irinotecan and temozolomide arm. In addition, a complete response was reported in an Ewing sarcoma patient and partial responses were reported in one synovial sarcoma and four Ewing sarcoma patients [50]. A Phase 1/2 study of rucaparib in 56 patients with advanced solid tumors and 42 patients with germline BRCA1/2-mutant high-grade ovarian carcinoma has reported two complete responses, six partial responses, and 22 stable diseases in the solid tumor cohort and four complete responses, 21 partial responses, and 12 stable diseases in the BRCA1/2 cohort per RECIST [93]. A Phase 1b study of veliparib in combination with capecitabine plus radiotherapy in patients with locally advanced rectal cancer reported tumor downstaging after surgery in 71% of 31 evaluable patients, with a pathologic complete response in 29% of patients. An acceptable safety profile was reported, with a recommended phase 2 dose of 400 mg BID; the maximum tolerated dose was not reached [38]. A Phase 1 study of tazemetostat in 43 patients with solid tumors and 21 patients with B-cell non-Hodgkin lymphoma (NHL) has reported response rates of 5% (2/43) and 38% (8/21) in solid tumor and NHL patients, respectively. Grade 4 thrombocytopenia was the only dose-limiting toxicity observed [76].

Preclinical: A preclinical study has reported that niraparib treatment of microsatellite stable and instable colorectal cancer cell lines inhibits proliferation and enhances the anti-proliferative effects of SN-38 in vitro, as

well as further delays tumor regrowth when combined with irinotecan in vivo, compared with irinotecan treatment alone [56]. A preclinical study analyzing 93 colorectal carcinoma cell lines reported that eight exhibited sensitivity to PARPi treatment, and that among these eight cell lines, talazoparib demonstrated greater efficacy than olaparib, niraparib, veliparib, or rucaparib [162]. A preclinical study has reported that tazemetostat treatment decreased tumor growth in a colorectal carcinoma xenograft mouse model [29].

MSH2 N538fs*5

Gene: MSH2
Exon: 10
Nucleotide: NM_000251.3: g.47693895delA c.1613delA
Amino Acid: p.N538fs*5
Allelic Fraction: 18.0% (of 335 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Biomarker summary: MSH2-N538fs*5 is an inactivating mutation.

Clinical relevance: MSH2 encodes MutS protein homolog 2 (Msh2), a member of the mismatch repair (MMR) gene family; defective MMR as a result of inactivating MSH2 mutation can result in microsatellite instability (MSI) [125, 51]. Germline mutations in MSH2 or genes encoding other mismatch repair proteins such as MLH1, MSH6, and PMS2 are associated with Lynch syndrome, which is a hereditary cancer-predisposition syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC) [111]. While there are currently no approved therapies directly addressing loss or mutation in MSH2, PD-1/PD-L1 inhibitors have been reported to be effective in tumors harboring mismatch repair defects; thus, a tumor with Msh2 inactivation may be sensitive to these therapies [97, 141, 23, 57].

Disease summary: Alterations in MSH2 or other mismatch repair genes (such as MLH1, MSH6, and PMS2) have been reported to underlie hereditary nonpolyposis colorectal cancer (HNPCC). Additionally, research suggests that carriers of MSH2 mutations have an increased risk of developing colorectal cancer [79, 44, 1].

Molecular function: The MSH2 frameshift alteration reported here is expected to effectively truncate the Msh2 protein, resulting in the loss of a portion of the C-terminal domain, which is involved in MutS dimer formation (InterPro). Truncating mutations in the C-terminal domain have been reported as germline alterations in Lynch syndrome families, and truncation of the C-terminal 60 amino acids of Msh2 has been reported to result in reduced mismatch repair capacity [191]. Therefore, this mutation is predicted to lead to a loss of Msh2 function.

Incidence: MSH2 mutations have been reported in 5.0% (208/4169) of Colorectal carcinoma (CRC) samples analyzed in COSMIC (May 2020). MSH2 mutations have been reported in 1.9-2.2% of Colorectal carcinoma (CRC) samples (cBioPortal for Cancer Genomics, May 2020). Scientific studies have reported MSH2 mutation in approximately 2-12% of colorectal carcinoma specimens analyzed [202, 2, 84, 132].

Role in disease: Defective mismatch repair (MMR), occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium and stomach cancers [117]. MSH2 alterations have been reported to underlie hereditary nonpolyposis colorectal cancer (HNPCC) and research suggests that carriers of MSH2 mutations have an increased risk of developing colorectal cancer [79, 44, 1].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: While there are currently no approved therapies directly addressing loss or mutation in MSH2, PD-1/PD-L1 inhibitors have been reported to be effective in tumors harboring mismatch repair defects; thus, a tumor with Msh2 inactivation may be sensitive to PD-1/PD-L1 inhibitors [97, 141, 23, 57].

Drug resistance: None.

Approved Drugs: None.

Phase 3: The second interim analysis of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 patients with MSI-high or deficient MMR metastatic colorectal carcinoma has reported a progression-free survival of 16.5 and 8.2 months, a confirmed overall response rate of 43.8% and 33.1%, an estimated restricted mean survival of 13.7 and 10.8 months, and grade 3-5 serious adverse events in 22% and 66% of patients treated with pembrolizumab or chemotherapy, respectively. Ongoing responses at 24 months were observed in 83% and 35% of patients treated with pembrolizumab or chemotherapy, respectively [8]. 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 [45].

Phase 2: 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 [116, 102, 97]. 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 [96]. 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

Variants of potential clinical significance (3)

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 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. The Phase 2 GERCOR NIPICOL study of nivolumab plus ipilimumab in 57 pretreated patients with MSI-H/dMMR metastatic colorectal cancer has reported 12-week disease control rate of 86.0% and 87.7%, and 12-month progression-free survival rate of 72.9% and 76.5%, according to RECIST 1.1 and iRECIST criteria, respectively. Overall response rate was 59.7% [33]. The Phase 2 NICHE study of neoadjuvant ipilimumab and nivolumab in early-stage colon cancer patients has reported pathological response in 100% (20 /20) of patients with MMR-deficient tumors and in 27% (4/15) of patients with MMR-proficient tumors [25]. 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 [129]. A Phase 2 study of nivolumab in combination with trifluridine/tipiracil in 18 patients with MSS colorectal carcinoma has reported 13 grade 3 or higher adverse events, no tumor responses, stable disease in eight and ten patients, and a median progression-free survival of 2.2 and 2.8 months per immune-related response criteria (irRC) and RECIST, respectively [131]. 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. 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 [198]. 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 1.9 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 [28]. A Phase 2 study of durvalumab and trametinib in 29 microsatellite stable metastatic colorectal cancer patients has reported objective response in 3.4% and stable disease in 24% of patients. No grade 4 treatment-related adverse events were observed. 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%. The Phase 2 CAVE study of avelumab and cetuximab in RAS wild-type metastatic colorectal carcinoma patients with response to first-line chemotherapy in combination with anti-Egfr therapy has reported complete response in 1.5%, partial response in 4.6%, and stable disease in 49.2% of 65 evaluable patients. Median progression-free and overall survival were 3.6 months and 13.1 months, respectively, and grade 3 adverse events were observed in 22% (16/77) of patients. A Phase 2 study of avelumab monotherapy in 33 metastatic or unresectable colorectal carcinoma patients with dMMR/MSI-H or POLE mutations has reported objective response rate of 24.2% and median progression-free survival and overall survival of 3.9 and 13.2 months, respectively [88]. A Phase 2 study of short-course radiation followed by mFOLFOX6 with avelumab in 13 patients with locally advanced rectal cancer has reported pathologic complete response (pCR) in 3/12 and near pCR in 3/12 evaluable patients. No grade 4 serious adverse events were observed [156].

Phase 1: 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. 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.

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

MSH2 N835fs*4

Gene: MSH2
Exon: 15
Nucleotide:

Biomarker summary: MSH2-N835fs*4 is an inactivating mutation.

Variants of potential clinical significance (3)

NM_000251.3:
g.47707877_4770788
3delCTAATTT
c.2502_2508delTAAT
TTC
Amino Acid: p.N835fs*4
Allelic Fraction: 35.0% (of 421 reads)
Classification: Tier 2C
Assessment: Pathogenic

Clinical relevance: MSH2 encodes MutS protein homolog 2 (Msh2), a member of the mismatch repair (MMR) gene family; defective MMR as a result of inactivating MSH2 mutation can result in microsatellite instability (MSI) [125, 51]. Germline mutations in MSH2 or genes encoding other mismatch repair proteins such as MLH1, MSH6, and PMS2 are associated with Lynch syndrome, which is a hereditary cancer-predisposition syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC) [111]. While there are currently no approved therapies directly addressing loss or mutation in MSH2, PD-1/PD-L1 inhibitors have been reported to be effective in tumors harboring mismatch repair defects; thus, a tumor with Msh2 inactivation may be sensitive to these therapies [97, 141, 23, 57].

Disease summary: Alterations in MSH2 or other mismatch repair genes (such as MLH1, MSH6, and PMS2) have been reported to underlie hereditary nonpolyposis colorectal cancer (HNPCC). Additionally, research suggests that carriers of MSH2 mutations have an increased risk of developing colorectal cancer [79, 44, 1].

Molecular function: The MSH2 frameshift alteration reported here is expected to effectively truncate the Msh2 protein, resulting in the loss of a portion of the C-terminal domain, which is involved in MutS dimer formation (InterPro). Truncating mutations in the C-terminal domain have been reported as germline alterations in Lynch syndrome families, and truncation of the C-terminal 60 amino acids of Msh2 has been reported to result in reduced mismatch repair capacity [191]. Therefore, this mutation is predicted to lead to a loss of Msh2 function.

Incidence: MSH2 mutations have been reported in 5.0% (208/4169) of Colorectal carcinoma (CRC) samples analyzed in COSMIC (May 2020). MSH2 mutations have been reported in 1.9-2.2% of Colorectal carcinoma (CRC) samples (cBioPortal for Cancer Genomics, May 2020). Scientific studies have reported MSH2 mutation in approximately 2-12% of colorectal carcinoma specimens analyzed [202, 2, 84, 132].

Role in disease: Defective mismatch repair (MMR), occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium and stomach cancers [117]. MSH2 alterations have been reported to underlie hereditary nonpolyposis colorectal cancer (HNPCC) and research suggests that carriers of MSH2 mutations have an increased risk of developing colorectal cancer [79, 44, 1].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: While there are currently no approved therapies directly addressing loss or mutation in MSH2, PD-1/PD-L1 inhibitors have been reported to be effective in tumors harboring mismatch repair defects; thus, a tumor with Msh2 inactivation may be sensitive to PD-1/PD-L1 inhibitors [97, 141, 23, 57].

Drug resistance: None.

Approved Drugs: None.

Phase 3: The second interim analysis of the Phase 3 KEYNOTE-177 study comparing 1:1 pembrolizumab with investigator choice of chemotherapy in 307 patients with MSI-high or deficient MMR metastatic colorectal carcinoma has reported a progression-free survival of 16.5 and 8.2 months, a confirmed overall response rate of 43.8% and 33.1%, an estimated restricted mean survival of 13.7 and 10.8 months, and grade 3-5 serious adverse events in 22% and 66% of patients treated with pembrolizumab or chemotherapy, respectively. Ongoing responses at 24 months were observed in 83% and 35% of patients treated with pembrolizumab or chemotherapy, respectively [8]. 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 [45].

Phase 2: 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 [116, 102, 97]. 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 [96]. 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 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. The Phase 2 GERCOR NIPICOL study of nivolumab plus ipilimumab in 57 pretreated patients with MSI-H/dMMR metastatic colorectal cancer has reported 12-week disease control rate of 86.0% and 87.7%,

Variants of potential clinical significance (3)

and 12-month progression-free survival rate of 72.9% and 76.5%, according to RECIST 1.1 and iRECIST criteria, respectively. Overall response rate was 59.7% [33]. The Phase 2 NICHE study of neoadjuvant ipilimumab and nivolumab in early-stage colon cancer patients has reported pathological response in 100% (20 /20) of patients with MMR-deficient tumors and in 27% (4/15) of patients with MMR-proficient tumors [25]. 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 [129]. A Phase 2 study of nivolumab in combination with trifluridine/tipiracil in 18 patients with MSS colorectal carcinoma has reported 13 grade 3 or higher adverse events, no tumor responses, stable disease in eight and ten patients, and a median progression-free survival of 2.2 and 2.8 months per immune-related response criteria (irRC) and RECIST, respectively [131]. 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. 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 [198]. 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 1.9 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 [28]. A Phase 2 study of durvalumab and trametinib in 29 microsatellite stable metastatic colorectal cancer patients has reported objective response in 3.4% and stable disease in 24% of patients. No grade 4 treatment-related adverse events were observed. 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%. The Phase 2 CAVE study of avelumab and cetuximab in RAS wild-type metastatic colorectal carcinoma patients with response to first-line chemotherapy in combination with anti-Egfr therapy has reported complete response in 1.5%, partial response in 4.6%, and stable disease in 49.2% of 65 evaluable patients. Median progression-free and overall survival were 3.6 months and 13.1 months, respectively, and grade 3 adverse events were observed in 22% (16/77) of patients. A Phase 2 study of avelumab monotherapy in 33 metastatic or unresectable colorectal carcinoma patients with dMMR/MSI-H or POLE mutations has reported objective response rate of 24.2% and median progression-free survival and overall survival of 3.9 and 13.2 months, respectively [88]. A Phase 2 study of short-course radiation followed by mFOLFOX6 with avelumab in 13 patients with locally advanced rectal cancer has reported pathologic complete response (pCR) in 3/12 and near pCR in 3/12 evaluable patients. No grade 4 serious adverse events were observed [156].

Phase 1: 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. 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.

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

Variants of uncertain significance (6)

Gene	Variant	Allelic fraction	Classification
DNMT3A	c.557C>T p.P186L	20.0% (of 606 reads)	Tier 3, Uncertain Significance
INPP4A	c.2792G>A p.C931Y	22.0% (of 459 reads)	Tier 3, Uncertain Significance
NTRK1	c.253C>T p.R85C	16.0% (of 680 reads)	Tier 3, Uncertain Significance
PAX8	c.172G>A p.V58I	17.0% (of 1014 reads)	Tier 3, Uncertain Significance
PIK3C2B	c.1771G>A p.A591T	18.0% (of 997 reads)	Tier 3, Uncertain Significance
RAD54L	c.1345T>C p.S449P	49.0% (of 790 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested (523)

DICER1, DHX15, DDX41, DDR2, DCUN1D1, DAXX, CYLD, CXCR4, CUX1, CUL3, CTNNB1, CTNNA1, CTLA4, CTCF, CSNK1A1, CSF3R, CSF1R, CRLF2, CRKL, CREBBP, CIC, CHEK2, CHEK1, CHD4, CHD2, CENPA, CEBPA, CDKN2C, CDKN2B, CDKN2A, CDKN1B, CDKN1A, CDK8, CDK6, CDK4, CDK12, CDH1, CDC73, CD79B, CD79A, CD74, CD276, CD274, CCNE1, CCND3, CCND2, CCND1, CBL, CBFB, CASP8, CARD11, CALR, BTK, BTG1, BRIP1, BRD4, BRCA2, BRCA1, BRAF, BMPR1A, BLM, BIRC3, BCR, BCORL1, BCOR, BCL6, BCL2L2, BCL2L11, BCL2L1, BCL2, BCL10, BBC3, BARD1, BAP1, B2M, AXL, AXIN2, AXIN1, AURKB, AURKA, ATRX, ATR, ATM, ASXL2, ASXL1, ARID5B, ARID2, ARID1B, ARID1A, ARFRP1, ARAF, AR, APC, ANKRD26, ANKRD11, ALOX12B, ALK, AKT3, AKT2, AKT1, ACVR1B, ACVR1, ABL2, ABL1, H3-5, H3-3B, H3-3A, GSK3B, GRM3, GRIN2A, GREM1, GPS2, ADGRA2, GNAS, GNAQ, GNA13, GNA11, GLI1, GID4, GEN1, GATA6, GATA4, GATA3, GATA2, GATA1, GABRA6, FYN, FUBP1, FRS2, FOXP1, FOXO1, FOXL2, FOXA1, FLT4, FLT3, FLT1, FLI1, FLCN, FH, FGFR4, FGFR3, FGFR2, FGFR1, FGF9, FGF8, FGF7, FGF6, FGF5, FGF4, FGF3, FGF23, FGF2, FGF19, FGF14, FGF10, FGF1, FBXW7, FAT1, FAS, FANCL, FANCI, FANCG, FANCF, FANCE, FANCD2, FANCC, FANCA, TENT5C, ABRAXAS1, AMER1, EZH2, EWSR1, ETV6, ETV5, ETV4, ETV1, ETS1, ESR1, ERRFI1, ERG, ERCC5, ERCC4, ERCC3, ERCC2, ERCC1, ERBB4, ERBB3, ERBB2, EPHB1, EPHA7, EPHA5, EPHA3, EPCAM, EP300, EMSY, EML4, EIF4E, EIF4A2, EIF1AX, EGFR, EGFL7, EED, E2F3, DOT1L, DNMT3B, DNMT3A, DNMT1, DNAJB1, DIS3, MST1R, MST1, MSH6, MSH3, MSH2, MRE11, MPL, MLLT3, KMT2A, MLH1, MITF, MGA, MET, MEN1, MEF2B, MED12, MDM4, MDM2, MDC1, MCL1, MAX, MAPK3, MAPK1, MAP3K4, MAP3K14, MAP3K13, MAP3K1, MAP2K4, MAP2K2, MAP2K1, MALT1, MAGI2, LZTR1, LYN, LRP1B, LMO1, LATS2, LATS1, LAMP1, KRAS, KMT2D, KMT2C, KMT2B, KLHL6, KLF4, KIT, KIF5B, KEL, KEAP1, KDR, KDM6A, KDM5C, KDM5A, KAT6A, JUN, JAK3, JAK2, JAK1, IRS2, IRS1, IRF4, IRF2, INSR, INPP4B, INPP4A, INHBA, INHA, IL7R, IL10, IKZF1, IKBKE, IGF2, IGF1R, IGF1, IFNGR1, IDH2, IDH1, ID3, ICOSLG, HSP90AA1, HSD3B1, HRAS, HOXB13, HNRNPK, HNF1A, HLA-C, HLA-B, HLA-A, H3-4, H3C13, H3C14, H3C15, H3C12, H3C11, H3C10, H3C8, H3C7, H3C6, H3C4, H3C3, H3C2, H3C1, H2BC5, H1-2, HGF, RBM10, RB1, RASA1, RARA, RANBP2, RAF1, RAD54L, RAD52, RAD51D, RAD51C, RAD51B, RAD51, RAD50, RAD21, RAC1, RAB35, QKI, PTPRT, PTPRS, PTPRD, PTPN11, PTEN, PTCH1, PRSS8, PRKDC, PRKCI, PRKAR1A, PREX2, PRDM1, PPP6C, PPP2R2A, PPP2R1A, PPM1D, PPARG, POLE, POLD1, PNRC1, PMS2, PMS1, PMAIP1, PLK2, PLCG2, PIM1, PIK3R3, PIK3R2, PIK3R1, PIK3CG, PIK3CD, PIK3CB, PIK3CA, PIK3C3, PIK3C2G, PIK3C2B, PHOX2B, PHF6, PGR, PDPK1, PDK1, PDGFRB, PDGFRA, PDCD1LG2, PDCD1, PBRM1, PAX8, PAX7, PAX5, PAX3, PARP1, PRKN, PALB2, PAK5, PAK3, PAK1, NUTM1, NUP93, NTRK3, NTRK2, NTRK1, NSD1, NRG1, NRAS, NPM1, NOTCH4, NOTCH3, NOTCH2, NOTCH1, NKX3-1, NKX2-1, NFKBIA, NFE2L2, NF2, NF1, NEGR1, NCOR1, NCOA3, NBN, NAB2, MYOD1, MYD88, MYCN, MYCL, MYC, MYB, MUTYH, MTOR, ZRSR2, ZNF703, ZNF217, ZFHX3, ZBTB7A, ZBTB2, YES1, YAP1, XRCC2, XPO1, XIAP, WT1, CCN6, VTCN1, VHL, VEGFA, U2AF1, TSHR, TSC2, TSC1, TRAF7, TRAF2, TP63, TP53, TOP2A, TOP1, TNFRSF14, TNFAIP3, TMPRSS2, TMEM127, TGFBR2, TGFBR1, TFRC, TFE3, TET2, TET1, TERT, TERC, TCF7L2, TCF3, ELOC, TBX3, TAF1, SYK, SUZ12, SUFU, STK40, STK11, STAT5B, STAT5A, STAT4, STAT3, STAG2, STAG1, SRSF2, SRC, SPTA1, SPOP, SPEN, SOX9, SOX2, SOX17, SOX10, SOCS1, SNCAIP, SMO, SMC3, SMC1A, SMARCD1, SMARCB1, SMARCA4, SMAD4, SMAD3, SMAD2, SLX4, SLIT2, SHQ1, SH2D1A, SH2B3, SF3B1, SETD2, SETBP1, SDHD, SDHC, SDHB, SDHAF2, SDHA, RYBP, RUNX1T1, RUNX1, RPTOR, RPS6KB2, RPS6KB1, RPS6KA4, ROS1, RNF43, RIT1, RICTOR, RHOA, RHEB, COP1, RET, REL, RECQL4

Methods and limitations

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (7.1.20210316), 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 (2021-03-18 14:15:50.073), 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 (2020.4), 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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