Root Category

Your organization's address

Tel: Your organization's phone

Sample:	Coriell-NA12877_S1_L001_R1_001	**Predicted gender:**	male(p=2.60724e-06)
Phenotypes	Hydrocephalus	**Diseases**	Syndromic Disease

Sample Coriell-NA12877_S1_L001_R1_001 Report

NM_000492.3:c.1585-1G>A (Pathogenic)

This variant is at position 28,083 of the 11th intron of transcript NM_000492.3, located on the positive strand of chromosome 7q31.2.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Coding: c.1585-1G>A	CFTR	intron 11 of 26 position 28083 of 28083	SNV	rs76713772	Heterozygous	0.00007176	32

NM_002016.1:c.8392C>T(p.Gln2798Ter) (Likely pathogenic)

This variant is at position 8,254 of the third exon of transcript NM_002016.1, located on the negative strand of chromosome 1q21.3. It is a nonsense substitution, as it introduces a stop codon at protein position 2,798.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Protein: Q2798* (p.Gln2798Ter) **HGVS Coding:** c.8392C>T	FLG,FLG-AS1	exon 3 of 3 position 8254 of 12573	SNV	rs752088825	Heterozygous	0.00000398	295

NM_002769.5:c.166C>T(p.Gln56Ter) (Pathogenic)

This variant is at position 126 of the second exon of transcript NM_002769.5, located on the positive strand of chromosome 7q34. It is a nonsense substitution, as it introduces a stop codon at protein position 56.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Protein: Q56*(p.Gln56Ter) **HGVS Coding:** c.166C>T	PRSS1	exon 2 of 5 position 126 of 160	SNV	rs147366981	Heterozygous	0.00023120	17

NM_004333.6:c.2128-28dupT (Uncertain significance)

This variant is between positions 5,014 and 5,015 of the 17th intron of transcript NM_004333.6, located on the negative strand of chromosome 7q34.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Coding: c.2128-28dupT	BRAF	intron 17 of 17 before position 5015 of 5041	Insertion (1)	rs60814637, rs397813649	Homozygous variant		24

Primary finding

NM_000492.3:c.1585-1G>A (Pathogenic)

This variant is at position 28,083 of the 11th intron of transcript NM_000492.3, located on the positive strand of chromosome 7q31.2.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Coding: c.1585-1G>A	CFTR	intron 11 of 26 position 28083 of 28083	SNV	rs76713772	Heterozygous	0.00007176	32

CFTR (Synonyms: ABC35, CFTR/MRP, MRP7, TNR-CFTR, dJ760C5.1)

cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)

Diseases: **Syndromic Disease**

Phenotypes: **Hydrocephalus**

Clinical Genomic Database (09_sep_2019)

Condition	Cystic fibrosis	**Inheritance**	AR
Comments		**Intervention categories**	Allergy/Immunology/Infectious, Endocrine, Gastrointestinal, Pulmonary

The *CFTR* gene provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. The channel transports negatively charged particles called chloride ions into and out of cells. The transport of chloride ions helps control the movement of water in tissues, which is necessary for the production of thin, freely flowing mucus. Mucus is a slippery substance that lubricates and protects the lining of the airways, digestive system, reproductive system, and other organs and tissues.

The CFTR protein also regulates the function of other channels, such as those that transport positively charged particles called sodium ions across cell membranes. These channels are necessary for the normal function of organs such as the lungs and pancreas.

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Conditions

Congenital Bilateral Absence Of The Vas Deferens

Congenital bilateral absence of the vas deferens occurs in males when the tubes that carry sperm out of the testes (the vas deferens) fail to develop properly. Although the testes usually develop and function normally, sperm cannot be transported through the vas deferens to become part of semen. As a result, men with this condition are unable to father children (infertile) unless they use assisted reproductive technologies. This condition has not been reported to affect sex drive or sexual performance.

This condition can occur alone or as a sign of cystic fibrosis, an inherited disease of the mucus glands. Cystic fibrosis causes progressive damage to the respiratory system and chronic digestive system problems. Many men with congenital bilateral absence of the vas deferens do not have the other characteristic features of cystic fibrosis; however, some men with this condition may experience mild respiratory or digestive problems.

Cystic Fibrosis

Cystic fibrosis is an inherited disease characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The disorder's most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems. The features of the disorder and their severity varies among affected individuals.

Mucus is a slippery substance that lubricates and protects the linings of the airways, digestive system, reproductive system, and other organs and tissues. In people with cystic fibrosis, the body produces mucus that is abnormally thick and sticky. This abnormal mucus can clog the airways, leading to severe problems with breathing and bacterial infections in the lungs. These infections cause chronic coughing, wheezing, and inflammation. Over time, mucus buildup and infections result in permanent lung damage, including the formation of scar tissue (fibrosis) and cysts in the lungs.

Most people with cystic fibrosis also have digestive problems. Some affected babies have meconium ileus, a blockage of the intestine that occurs shortly after birth. Other digestive problems result from a buildup of thick, sticky mucus in the pancreas. The pancreas is an organ that produces insulin (a hormone that helps control blood sugar levels). It also makes enzymes that help digest food. In people with cystic fibrosis, mucus often damages the pancreas, impairing its ability to produce insulin and digestive enzymes. Problems with digestion can lead to diarrhea, malnutrition, poor growth, and weight loss. In adolescence or adulthood, a shortage of insulin can cause a form of diabetes known as cystic fibrosis-related diabetes mellitus (CFRDM).

Cystic fibrosis used to be considered a fatal disease of childhood. With improved treatments and better ways to manage the disease, many people with cystic fibrosis now live well into adulthood. Adults with cystic fibrosis experience health problems affecting the respiratory, digestive, and reproductive systems. Most men with cystic fibrosis have congenital bilateral absence of the vas deferens (CBAVD), a condition in which the tubes that carry sperm (the vas deferens) are blocked by mucus and do not develop properly. Men with CBAVD are unable to father children (infertile) unless they undergo fertility treatment. Women with cystic fibrosis may experience complications in pregnancy.

Hereditary Pancreatitis

Hereditary pancreatitis is a genetic condition characterized by recurrent episodes of inflammation of the pancreas (pancreatitis). The pancreas produces enzymes that help digest food, and it also produces insulin, a hormone that controls blood sugar levels in the body. Episodes of pancreatitis can lead to permanent tissue damage and loss of pancreatic function.

Signs and symptoms of this condition usually begin in late childhood with an episode of acute pancreatitis. A sudden (acute) attack can cause abdominal pain, fever, nausea, or vomiting. An episode typically lasts from one to three days, although some people may experience severe episodes that last longer. Hereditary pancreatitis progresses to recurrent acute pancreatitis with multiple episodes of acute pancreatitis that recur over a period of at least a year; the number of episodes a person experiences varies. Recurrent acute pancreatitis leads to chronic pancreatitis, which occurs when the pancreas is persistently inflamed. Chronic pancreatitis usually develops by early adulthood in affected individuals. Signs and symptoms of chronic pancreatitis include occasional or frequent abdominal pain of varying severity, flatulence, and bloating. Many individuals with hereditary pancreatitis also develop abnormal calcium deposits in the pancreas (pancreatic calcifications) by early adulthood.

Years of inflammation damage the pancreas, causing the formation of scar tissue (fibrosis) in place of functioning pancreatic tissue. Pancreatic fibrosis leads to the loss of pancreatic function in many affected individuals. This loss of function can impair the production of digestive enzymes and disrupt normal digestion, leading to fatty stool (steatorrhea), weight loss, and protein and vitamin deficiencies. Because of a decrease in insulin production due to a loss of pancreatic function, about a quarter of individuals with hereditary pancreatitis will develop type 1 diabetes mellitus by mid-adulthood; the risk of developing diabetes increases with age.

Chronic pancreatic inflammation and damage to the pancreas increase the risk of developing pancreatic cancer. The risk is particularly high in people with hereditary pancreatitis who also smoke, use alcohol, have type 1 diabetes mellitus, or have a family history of cancer. In affected individuals who develop pancreatic cancer, it is typically diagnosed in mid-adulthood.

Complications from pancreatic cancer and type 1 diabetes mellitus are the most common causes of death in individuals with hereditary pancreatitis, although individuals with this condition are thought to have a normal life expectancy.

CFTR related drugs

Drug name	Attributes	Disease
Felodipine Interaction type: activator Approved: Yes	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Bumetanide Interaction type: antagonist Approved: Yes		
Chembl1372588 Interaction type: activator Approved: No	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Chembl1949980 Interaction type: activator Approved: No	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	

Crofelemer Interaction type: antagonist, inhibitor Approved: Yes	*Endogenous Drug*: False *Specific Action Of The Ligand*: Inhibition *Direct Interaction*: True *Mechanism Of Interaction*: Cystic fibrosis transmembrane conductance regulator inhibitor *Direct Interaction*: yes *Trial Name*: crofelemer *Novel Drug Target*: Established target	
Capsaicin Interaction type: activator Approved: Yes	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Glyburide Interaction type: channel blocker, antagonist Approved: Yes	*Specific Action Of The Ligand*: None *Endogenous Drug*: False	
Chembl177991 Interaction type: activator Approved: No	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Chembl461939 Interaction type: channel blocker Approved: No	*Interaction Context*: intracellular *Specific Action Of The Ligand*: None *Details Of Interaction*: intracellular application prolongs mean closed time *Endogenous Drug*: False *Direct Interaction*: False	
Chembl1230989 Approved: No		
Qbw251 Interaction type: activator Approved: No	*Mechanism Of Interaction*: Cystic fibrosis transmembrane conductance regulator activator *Direct Interaction*: yes	
Retinol Approved: Yes		
Tezacaftor Approved: No	*Mechanism Of Interaction*: Cystic fibrosis transmembrane conductance regulator positive modulator *Direct Interaction*: yes	
Nimodipine Interaction type: activator Approved: Yes	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Genistein Interaction type: activator Approved: No	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Chembl1221576 Interaction type: channel blocker Approved: No	*Interaction Context*: extracellular *Specific Action Of The Ligand*: None *Endogenous Drug*: False	
Apigenin Interaction type: activator Approved: No	*Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False	
Lumacaftor Interaction type: modulator Approved: Yes	*Mechanism Of Interaction*: Cystic fibrosis transmembrane conductance regulator stabiliser *Direct Interaction*: yes *Trial Name*: VX-809 *Novel Drug Target*: Established target *Trial Name*: VX-809 + VX-770 *Combination Therapy*: Ivacaftor, Lumacaftor	

Ivacaftor Interaction type: potentiator, activator Approved: Yes	*Combination Therapy*: Ivacaftor, Lumacaftor *Specific Action Of The Ligand*: Potentiation *Endogenous Drug*: False *Mechanism Of Interaction*: Cystic fibrosis transmembrane conductance regulator positive modulator *Direct Interaction*: yes *Trial Name*: VX-770 *Novel Drug Target*: Established target *Trial Name*: VX-809 + VX-770	
Dexfosfoserine Approved: No		

Secondary finding

NM_002769.5:c.166C>T(p.Gln56Ter) (Pathogenic)

This variant is at position 126 of the second exon of transcript NM_002769.5, located on the positive strand of chromosome 7q34. It is a nonsense substitution, as it introduces a stop codon at protein position 56.

Mutation	Gene(s)	Exon	Variant Type	RS ID	Zygosity	Frequency	Coverage
HGVS Protein: Q56* (p.Gln56Ter) **HGVS Coding:** c.166C>T	PRSS1	exon 2 of 5 position 126 of 160	SNV	rs147366981	Heterozygous	0.00023120	17

BRAF (Synonyms: BRAF1)

B-Raf proto-oncogene, serine/threonine kinase

Phenotypes: **Hydrocephalus**

Clinical Genomic Database (09_sep_2019)

Condition	Noonan syndrome; Cardiofaciocutaneous syndrome 1; LEOPARD syndrome 3	**Inheritance**	AD
Comments	Conditions may be frequently clinically recognized due to characteristic facial features as well as other manifestations	**Intervention categories**	Cardiovascular, Hematologic, Oncologic

The *BRAF* gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell's nucleus. This protein is part of a signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions. Specifically, the RAS/MAPK pathway regulates the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (migration), and the self-destruction of cells (apoptosis). Chemical signaling through this pathway is essential for normal development before birth.

The *BRAF* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous.

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Conditions

Cardiofaciocutaneous Syndrome

Cardiofaciocutaneous syndrome is a disorder that affects many parts of the body, particularly the heart (cardio-), facial features (facio-), and the skin and hair (cutaneous). People with this condition also have delayed development and intellectual disability, usually ranging from moderate to severe.

Heart defects occur in most people with cardiofaciocutaneous syndrome. The heart problems most commonly associated with this condition include malformations of one of the heart valves that impairs blood flow from the heart to the lungs (pulmonic stenosis), a hole between the two upper chambers of the heart (atrial septal defect), and a form of heart disease that enlarges and weakens the heart muscle (hypertrophic cardiomyopathy).

Cardiofaciocutaneous syndrome is also characterized by distinctive facial features. These include a high forehead that narrows at the temples, a short nose, widely spaced eyes (ocular hypertelorism), outside corners of the eyes that point downward (down-slanting palpebral fissures), droopy eyelids (ptosis), a small

chin, and low-set ears. Overall, the face is broad and long, and the facial features are sometimes described as "coarse."

Skin abnormalities occur in almost everyone with cardiofaciocutaneous syndrome. Many affected people have dry, rough skin; dark-colored moles (nevi); wrinkled palms and soles; and a skin condition called keratosis pilaris, which causes small bumps to form on the arms, legs, and face. People with cardiofaciocutaneous syndrome also tend to have thin, dry, curly hair and sparse or absent eyelashes and eyebrows.

Infants with cardiofaciocutaneous syndrome typically have weak muscle tone (hypotonia), feeding difficulties, and a failure to grow and gain weight at the normal rate (failure to thrive). Additional features of this disorder in children and adults can include an unusually large head (macrocephaly), short stature, problems with vision, and seizures.

The signs and symptoms of cardiofaciocutaneous syndrome overlap significantly with those of two other genetic conditions, Costello syndrome and Noonan syndrome. The three conditions are distinguished by their genetic cause and specific patterns of signs and symptoms; however, it can be difficult to tell these conditions apart, particularly in infancy. Unlike Costello syndrome, which significantly increases a person's cancer risk, cancer does not appear to be a major feature of cardiofaciocutaneous syndrome.

Cholangiocarcinoma

Cholangiocarcinoma is a group of cancers that begin in the bile ducts. Bile ducts are branched tubes that connect the liver and gallbladder to the small intestine. They carry bile, which is a fluid that helps the body digest the fats in food. Bile is produced in the liver and stored in the gallbladder before being released in the small intestine after a person eats.

Cholangiocarcinoma is classified by its location in relation to the liver. Intrahepatic cholangiocarcinoma begins in the small bile ducts within the liver. This is the least common form of the disease, accounting for less than 10 percent of all cases. Perihilar cholangiocarcinoma (also known as a Klatskin tumor) begins in an area called the hilum, where two major bile ducts join and leave the liver. It is the most common form of the disease, accounting for more than half of all cases. The remaining cases are classified as distal cholangiocarcinomas, which begin in bile ducts outside the liver. The perihilar and distal forms of the disease, which both occur outside the liver, are sometimes grouped together and called extrahepatic cholangiocarcinoma.

The three types of cholangiocarcinoma do not usually cause any symptoms in their early stages, and this cancer is usually not diagnosed until it has already spread beyond the bile ducts to other tissues. Symptoms often result when bile ducts become blocked by the tumor. The most common symptom is jaundice, which is a yellowing of the skin and the whites of the eyes. Other symptoms can include itching, dark-colored urine, loss of appetite, unintentional weight loss, abdominal pain, and light-colored and greasy stools. These symptoms are described as "nonspecific" because they can be features of many different diseases.

Most people who develop cholangiocarcinoma are older than 65. Because this cancer is often not discovered until it has already spread, it can be challenging to treat effectively. Affected individuals can survive for several months to several years after diagnosis.

Erdheim-Chester Disease

Erdheim-Chester disease is a rare type of slow-growing blood cancer called a histiocytic neoplasm, which results in overproduction of cells called histiocytes. Histiocytes normally function to destroy foreign substances and protect the body from infection. In Erdheim-Chester disease, the excess production of histiocytes (histiocytosis) leads to inflammation that can damage organs and tissues throughout the body, causing them to become thickened, dense, and scarred (fibrotic); this tissue damage may lead to organ failure.

People with Erdheim-Chester disease often have bone pain, especially in the lower legs and upper arms, due to an abnormal increase in bone density (osteosclerosis). Damage to the pituitary gland (a structure at the base of the brain that produces several hormones, including a hormone that controls the amount of water released in the urine) may result in hormonal problems such as a condition called diabetes insipidus that leads to excessive urination. Abnormally high pressure of the cerebrospinal fluid within the skull (intracranial hypertension) caused by accumulation of histiocytes in the brain may result in headaches, seizures, cognitive impairment, or problems with movement or sensation. People with this condition can also have shortness of breath, heart or kidney disease, protruding eyes (exophthalmos), skin growths, or inability to conceive a child (infertility). Affected individuals may also experience fever, night sweats, fatigue, weakness, and weight loss.

The signs and symptoms of Erdheim-Chester disease usually appear between the ages of 40 and 60, although the disorder can occur at any age. The severity of the condition varies widely; some affected individuals have few or no associated health problems, while others have severe complications that can be life-threatening.

Gastrointestinal Stromal Tumor

A gastrointestinal stromal tumor (GIST) is a type of tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine. The tumors are thought to grow from specialized cells found in the gastrointestinal tract called interstitial cells of Cajal (ICCs) or precursors to these cells. GISTs are usually found in adults between ages 40 and 70; rarely, children and young adults develop these tumors. The tumors can be cancerous (malignant) or noncancerous (benign).

Small tumors may cause no signs or symptoms. However, some people with GISTs may experience pain or swelling in the abdomen, nausea, vomiting, loss of appetite, or weight loss. Sometimes, tumors cause bleeding, which may lead to low red blood cell counts (anemia) and, consequently, weakness and tiredness. Bleeding into the intestinal tract may cause black and tarry stools, and bleeding into the throat or stomach may cause vomiting of blood.

Affected individuals with no family history of GIST typically have only one tumor (called a sporadic GIST). People with a family history of GISTs (called familial GISTs) often have multiple tumors and additional signs or symptoms, including noncancerous overgrowth (hyperplasia) of other cells in the gastrointestinal tract and patches of dark skin on various areas of the body. Some affected individuals have a skin condition called urticaria pigmentosa (also known as cutaneous mastocytosis), which is characterized by raised patches of brownish skin that sting or itch when touched.

Giant Congenital Melanocytic Nevus

Giant congenital melanocytic nevus is a skin condition characterized by an abnormally dark, noncancerous skin patch (nevus) that is composed of pigment-producing cells called melanocytes. It is present from birth (congenital) or is noticeable soon after birth. The nevus may be small in infants, but it will usually grow at the same rate the body grows and will eventually be at least 40 cm (15.75 inches) across. The nevus can appear anywhere on the body, but it is more often found on the trunk or limbs. The color ranges from tan to black and can become darker or lighter over time. The surface of a nevus can be flat, rough, raised, thickened, or bumpy; the surface can vary in different regions of the nevus, and it can change over time. The skin of the nevus is often dry and prone to irritation and itching (dermatitis). Excessive hair growth (hypertrichosis) can occur within the nevus. There is often less fat tissue under the skin of the nevus; the skin may

appear thinner there than over other areas of the body.

People with giant congenital melanocytic nevus may have more than one nevus (plural: nevi). The other nevi are often smaller than the giant nevus. Affected individuals may have one or two additional nevi or multiple small nevi that are scattered over the skin; these are known as satellite or disseminated nevi.

Affected individuals may feel anxiety or emotional stress due to the impact the nevus may have on their appearance and their health. Children with giant congenital melanocytic nevus can develop emotional or behavior problems.

Some people with giant congenital melanocytic nevus develop a condition called neurocutaneous melanosis, which is the presence of pigment-producing skin cells (melanocytes) in the tissue that covers the brain and spinal cord. These melanocytes may be spread out or grouped together in clusters. Their growth can cause increased pressure in the brain, leading to headache, vomiting, irritability, seizures, and movement problems. Tumors in the brain may also develop.

Individuals with giant congenital melanocytic nevus have an increased risk of developing an aggressive form of skin cancer called melanoma, which arises from melanocytes. Estimates vary, but it is generally thought that people with giant congenital melanocytic nevus have a 5 to 10 percent lifetime risk of developing melanoma. Melanoma commonly begins in the nevus, but it can develop when melanocytes that invade other tissues, such as those in the brain and spinal cord, become cancerous. When melanoma occurs in people with giant congenital melanocytic nevus, the survival rate is low.

Other types of tumors can also develop in individuals with giant congenital melanocytic nevus, including soft tissue tumors (sarcomas), fatty tumors (lipomas), and tumors of the nerve cells (schwannomas).

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis is a disorder in which excess immune system cells called Langerhans cells build up in the body. Langerhans cells, which help regulate the immune system, are normally found throughout the body, especially in the skin, lymph nodes, spleen, lungs, liver, and bone marrow. In Langerhans cell histiocytosis, excess immature Langerhans cells usually form tumors called granulomas. Many researchers now consider Langerhans cell histiocytosis to be a form of cancer, but this classification remains controversial.

In approximately 80 percent of affected individuals, one or more granulomas develop in the bones, causing pain and swelling. The granulomas, which usually occur in the skull or the long bones of the arms or legs, may cause the bone to fracture.

Granulomas also frequently occur in the skin, appearing as blisters, reddish bumps, or rashes which can be mild to severe. The pituitary gland may also be affected; this gland is located at the base of the brain and produces hormones that control many important body functions. Without hormone supplementation, affected individuals may experience delayed or absent puberty or an inability to have children (infertility). In addition, pituitary gland damage may result in the production of excessive amounts of urine (diabetes insipidus) and dysfunction of another gland called the thyroid. Thyroid dysfunction can affect the rate of chemical reactions in the body (metabolism), body temperature, skin and hair texture, and behavior.

In 15 to 20 percent of cases, Langerhans cell histiocytosis affects the lungs, liver, or blood-forming (hematopoietic) system; damage to these organs and tissues may be life-threatening. Lung involvement, which appears as swelling of the small airways (bronchioles) and blood vessels of the lungs, results in stiffening of the lung tissue, breathing problems, and increased risk of infection. Hematopoietic involvement, which occurs when the Langerhans cells crowd out blood-forming cells in the bone marrow, leads to a general reduction in the number of blood cells (pancytopenia). Pancytopenia results in fatigue due to low numbers of red blood cells (anemia), frequent infections due to low numbers of white blood cells (neutropenia), and clotting problems due to low numbers of platelets (thrombocytopenia).

Other signs and symptoms that may occur in Langerhans cell histiocytosis, depending on which organs and tissues have Langerhans cell deposits, include swollen lymph nodes, abdominal pain, yellowing of the skin and whites of the eyes (jaundice), delayed puberty, protruding eyes, dizziness, irritability, and seizures. About 1 in 50 affected individuals experience deterioration of neurological function (neurodegeneration).

Langerhans cell histiocytosis is often diagnosed in childhood, usually between ages 2 and 3, but can appear at any age. Most individuals with adult-onset Langerhans cell histiocytosis are current or past smokers; in about two-thirds of adult-onset cases the disorder affects only the lungs.

The severity of Langerhans cell histiocytosis, and its signs and symptoms, vary widely among affected individuals. Certain presentations or forms of the disorder were formerly considered to be separate diseases. Older names that were sometimes used for forms of Langerhans cell histiocytosis include eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease.

In many people with Langerhans cell histiocytosis, the disorder eventually goes away with appropriate treatment. It may even disappear on its own, especially if the disease occurs only in the skin. However, some complications of the condition, such as diabetes insipidus or other effects of tissue and organ damage, may be permanent.

Lung Cancer

Lung cancer is a disease in which certain cells in the lungs become abnormal and multiply uncontrollably to form a tumor. Lung cancer may not cause signs or symptoms in its early stages. Some people with lung cancer have chest pain, frequent coughing, blood in the mucus, breathing problems, trouble swallowing or speaking, loss of appetite and weight loss, fatigue, or swelling in the face or neck. Additional symptoms can develop if the cancer spreads (metastasizes) into other tissues. Lung cancer occurs most often in adults in their sixties or seventies. Most people who develop lung cancer have a history of long-term tobacco smoking; however, the condition can occur in people who have never smoked.

Lung cancer is generally divided into two types, small cell lung cancer and non-small cell lung cancer, based on the size of the affected cells when viewed under a microscope. Non-small cell lung cancer accounts for 85 percent of lung cancer, while small cell lung cancer accounts for the remaining 15 percent.

Small cell lung cancer grows quickly and in more than half of cases the cancer has spread beyond the lung by the time the condition is diagnosed. Small cell lung cancer often metastasizes, most commonly to the liver, brain, bones, and adrenal glands (small hormone-producing glands located on top of each kidney). After diagnosis, most people with small cell lung cancer survive for about 1 year; less than seven percent survive 5 years.

Non-small cell lung cancer is divided into three main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma. Adenocarcinoma arises from the cells that line the small air sacs (alveoli) located throughout the lungs. Squamous cell carcinoma arises from squamous cells that line the passages leading from the windpipe (trachea) to the lungs (bronchi). Large cell carcinoma arises from epithelial cells that line the lungs. Large cell carcinoma encompasses non-small cell lung cancers that do not appear to be adenocarcinomas or squamous cell carcinomas. The 5-year survival rate for people with non-small cell lung cancer is usually between 11 and 17 percent; it can be lower or higher depending on the subtype and stage of the cancer.

Melanoma

Melanoma is a type of skin cancer that begins in pigment-producing cells called melanocytes. This cancer typically occurs in areas that are only occasionally sun-exposed; tumors are most commonly found on the back in men and on the legs in women. Melanoma usually occurs on the skin (cutaneous melanoma), but in about 5 percent of cases it develops in melanocytes in other tissues, including the eyes (uveal melanoma) or mucous membranes that line the body's cavities, such as the moist lining of the mouth (mucosal melanoma). Melanoma can develop at any age, but it most frequently occurs in people in their fifties to seventies and is becoming more common in teenagers and young adults.

Melanoma may develop from an existing mole or other normal skin growth that becomes cancerous (malignant); however, many melanomas are new growths. Melanomas often have ragged edges and an irregular shape. They can range from a few millimeters to several centimeters across. They can also be a variety of colors: brown, black, red, pink, blue, or white.

Most melanomas affect only the outermost layer of skin (the epidermis). If a melanoma becomes thicker and involves multiple layers of skin, it can spread to other parts of the body (metastasize).

A large number of moles or other pigmented skin growths on the body, generally more than 25, is associated with an increased risk of developing melanoma. Melanoma is also a common feature of genetic syndromes affecting the skin such as xeroderma pigmentosum. Additionally, individuals who have previously had melanoma are nearly nine times more likely than the general population to develop melanoma again. It is estimated that about 90 percent of individuals with melanoma survive at least 5 years after being diagnosed.

Multiple Myeloma

Multiple myeloma is a cancer that develops in the bone marrow, the spongy tissue found in the center of most bones. The bone marrow produces red blood cells, which carry oxygen throughout the body; white blood cells, which form the body's defenses (immune system); and platelets, which are necessary for blood clotting.

Multiple myeloma is characterized by abnormalities in plasma cells, a type of white blood cell. These abnormal cells multiply out of control, increasing from about one percent of cells in the bone marrow to the majority of bone marrow cells. The abnormal cells form tumors within the bone, causing bone pain and an increased risk of fractures. If the tumors interfere with nerves near the bones, numbness or weakness in the arms or legs can occur. Affected individuals may also experience a loss of bone tissue, particularly in the skull, spine, ribs, and pelvis. The deterioration of bone can result in an excess of calcium in the blood (hypercalcemia), which can lead to nausea and loss of appetite, excessive thirst, fatigue, muscle weakness, and confusion.

The abnormal plasma cells in multiple myeloma produce proteins that impair the development of normal blood cells. As a result, affected individuals may have a reduced number of red blood cells (anemia), which can cause fatigue, weakness, and unusually pale skin (pallor); a low number of white blood cells (leukopenia), which can result in a weakened immune system and frequent infections such as pneumonia; and a reduced number of platelets (thrombocytopenia), which can lead to abnormal bleeding and bruising. Kidney problems can also occur in this disorder, caused by hypercalcemia or by toxic proteins produced by the abnormal plasma cells.

People with multiple myeloma typically develop the disorder around age 65. Over time, affected individuals can develop life-threatening complications, but the rate at which this happens varies widely. Some affected individuals are diagnosed incidentally when tests are done for other purposes and do not experience symptoms for years.

Noonan Syndrome

Noonan syndrome is a condition that affects many areas of the body. It is characterized by mildly unusual facial features, short stature, heart defects, bleeding problems, skeletal malformations, and many other signs and symptoms.

People with Noonan syndrome have distinctive facial features such as a deep groove in the area between the nose and mouth (philtrum), widely spaced eyes that are usually pale blue or blue-green in color, and low-set ears that are rotated backward. Affected individuals may have a high arch in the roof of the mouth (high-arched palate), poor teeth alignment, and a small lower jaw (micrognathia). Many children with Noonan syndrome have a short neck, and both children and adults may have excess neck skin (also called webbing) and a low hairline at the back of the neck.

Between 50 and 70 percent of individuals with Noonan syndrome have short stature. At birth, they are usually a normal length and weight, but growth slows over time. Abnormal levels of growth hormone, a protein that is necessary for the normal growth of the body's bones and tissues, may contribute to the slow growth.

Individuals with Noonan syndrome often have either a sunken chest (pectus excavatum) or a protruding chest (pectus carinatum). Some affected people may also have an abnormal side-to-side curvature of the spine (scoliosis).

Most people with Noonan syndrome have some form of critical congenital heart disease. The most common heart defect in these individuals is a narrowing of the valve that controls blood flow from the heart to the lungs (pulmonary valve stenosis). Some have hypertrophic cardiomyopathy, which enlarges and weakens the heart muscle.

A variety of bleeding disorders have been associated with Noonan syndrome. Some affected individuals have excessive bruising, nosebleeds, or prolonged bleeding following injury or surgery. Rarely, women with Noonan syndrome who have a bleeding disorder have excessive bleeding during menstruation (menorrhagia) or childbirth.

Adolescent males with Noonan syndrome typically experience delayed puberty. They go through puberty starting at age 13 or 14 and have a reduced pubertal growth spurt that results in shortened stature. Most males with Noonan syndrome have undescended testes (cryptorchidism), which may contribute to infertility (inability to father a child) later in life. Females with Noonan syndrome can experience delayed puberty but most have normal puberty and fertility.

Noonan syndrome can cause a variety of other signs and symptoms. Most children diagnosed with Noonan syndrome have normal intelligence, but a few have special educational needs, and some have intellectual disability. Some affected individuals have vision or hearing problems. Affected infants may have feeding problems, which typically get better by age 1 or 2 years. Infants with Noonan syndrome may be born with puffy hands and feet caused by a buildup of fluid (lymphedema), which can go away on its own. Older individuals can also develop lymphedema, usually in the ankles and lower legs.

Some people with Noonan syndrome develop cancer, particularly those involving the blood-forming cells (leukemia). It has been estimated that children with Noonan syndrome have an eightfold increased risk of developing leukemia or other cancers over age-matched peers.

Noonan syndrome is one of a group of related conditions, collectively known as RASopathies. These conditions all have similar signs and symptoms and are caused by changes in the same cell signaling pathway. In addition to Noonan syndrome, the RASopathies include cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, Legius syndrome, and Noonan syndrome with multiple lentigines.

Noonan Syndrome With Multiple Lentigines

Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome) is a condition that affects many areas of the body. As the condition name suggests, Noonan syndrome with multiple lentigines is very similar to a condition called Noonan syndrome, and it can be difficult to tell the two disorders apart in early childhood. However, the features of these two conditions differ later in life. The characteristic features of Noonan syndrome with multiple lentigines include brown skin spots called lentigines that are similar to freckles, heart defects, widely spaced eyes (ocular hypertelorism), a sunken chest (pectus excavatum) or protruding chest (pectus carinatum), and short stature. These features vary, however, even among affected individuals in the same family. Not all individuals with Noonan syndrome with multiple lentigines have all the characteristic features of this condition.

The lentigines seen in Noonan syndrome with multiple lentigines typically first appear in mid-childhood, mostly on the face, neck, and upper body. Affected individuals may have thousands of small dark brown skin spots by the time they reach puberty. Unlike freckles, the appearance of lentigines has nothing to do with sun exposure. In addition to lentigines, people with this condition may have lighter brown skin spots called café-au-lait spots. Café-au-lait spots tend to develop before the lentigines, appearing within the first year of life in most affected people.

Of the people with Noonan syndrome with multiple lentigines who have heart defects, about 80 percent have hypertrophic cardiomyopathy, which is a thickening of the heart muscle that forces the heart to work harder to pump blood. The hypertrophic cardiomyopathy most often affects the lower left chamber of the heart (the left ventricle). Up to 20 percent of people with Noonan syndrome with multiple lentigines who have heart problems have a narrowing of the artery from the heart to the lungs (pulmonary stenosis).

People with Noonan syndrome with multiple lentigines can have a distinctive facial appearance. In addition to ocular hypertelorism, affected individuals may have droopy eyelids (ptosis), thick lips, and low-set ears. Affected individuals also usually have an abnormal appearance of the chest; they either have pectus excavatum or pectus carinatum.

At birth, people with Noonan syndrome with multiple lentigines are typically of normal weight and height, but in some, growth slows over time. This slow growth results in affected individuals being shorter than average, although less than half of people with Noonan syndrome with multiple lentigines have significantly short stature.

Other signs and symptoms of Noonan syndrome with multiple lentigines include hearing loss caused by abnormalities in the inner ear (sensorineural deafness), mild intellectual disability, and extra folds of skin on the back of the neck. Affected males often have genital abnormalities, which can include undescended testes (cryptorchidism) and a urethra that opens on the underside of the penis (hypospadias). These abnormalities may reduce the ability to have biological children (decreased fertility). Females with Noonan syndrome with multiple lentigines may have poorly developed ovaries and delayed puberty.

Noonan syndrome with multiple lentigines is one of a group of related conditions collectively known as RASopathies. These conditions all have similar signs and symptoms and are caused by changes in the same cell signaling pathway. In addition to Noonan syndrome with multiple lentigines, the RASopathies include Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, and Legius syndrome.

Variant	Evidence	Disease	Clinical Significance
V600E AMPLIFICATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 4	**Predictive** Level: E Status: accepted Direction: Supports COLO201 and COLO206F cells harboring BRAF V600E mutations were cloned to be MEK inhibitor (AZD6244 [selumetinib]) resistant. The mechanism of this resistance was shown to be amplification of the BRAF V600E gene. BRAF V600E amplification was observed in 1/11 colorectal cancer patient samples evaluated, indicating this subclone (28% of cells) would be MEK inhibitor resistant.	Colorectal Cancer	Resistance
AKAP9-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000356239.3 *Rating:* 4	**Diagnostic** Level: B Status: accepted Direction: Supports The AKAP9-BRAF fusion gene was found in 3/28 tumor samples of radiation-associated papillary thyroid carcinoma, and no samples of non-radiation associated papillary thyroid carcinoma. This fusion was associated with elevated BRAF kinase activity, similar to the V600E variant.	Thyroid Gland Papillary Carcinoma	Positive
AGK-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000355413.4 *Rating:* 2	**Predictive** Level: C Status: accepted Direction: Supports BRAF fusion AGK-BRAF was associated with decreased sensitivity to vemurafenib and increased sensitivity to sorafenib in-vitro. A single patient with this fusion showed durable response to sorafenib.	Melanoma	Sensitivity/Response

AGK-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000355413.4 *Rating:* 2	**Predictive** Level: D Status: accepted Direction: Supports A melanoma cell line with AGK-BRAF in-frame fusion showed decreased sensitivity towards Vemurafenib in comparison with BRAF mutated (V600E) cell lines.	Melanoma	Resistance
PAPSS1-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000265174.4 *Rating:* 3	**Predictive** Level: D Status: accepted Direction: Supports BRAF-fusion in "pan-negative" melanomas were identified in TCGA data. Cell-lines with PAPSS1-BRAF fusion were resistant to treatment with Vemurafenib.	Melanoma	Resistance
PAPSS1-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000265174.4 *Rating:* 3	**Predictive** Level: D Status: accepted Direction: Supports BRAF-fusion in "pan-negative" melanomas were identified in TCGA data. Cell-lines with a PAPSS1-BRAF fusion were resistant to treatment with Vemurafenib but sensitive to treatment with Trametinib. This fusion is believed to activate MAPK pathway signaling.	Melanoma	Sensitivity/Response
TRIM24-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000343526.4 *Rating:* 3	**Predictive** Level: D Status: accepted Direction: Supports A TRIM24-BRAF fusion was identified in a single patient with metastatic melanoma that was "pan-negative" for driver mutations. A cell-line (293H) ectopically expressing the TRIM24-BRAF fusion was found to be sensitive to the MEK-inhibitor Trametinib.	Melanoma	Sensitivity/Response
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 4	**Predictive** Level: D Status: accepted Direction: Supports In this screen of 218 solid cancer cell lines, BRAF mutations were predictive of response to the MEK inhibitor GSK1120212. 26 of these cell lines had the BRAF V600E mutation, one cell line had a G469A mutation, one had G596R mutation and one had an unspecified mutation. Also of note, in RAF/RAS mutant colon cancer cell lines, co-occurring PIK3CA/PTEN mutations led to a cytostatic response rather than a cytotoxic response.	Cancer	Sensitivity/Response
WILD TYPE *Representative Transcript:* ENST00000288602.6 *Rating:* 2	**Predictive** Level: B Status: accepted Direction: Supports Phase I expansion and pharmacodynamic study of the oral MEK inhibitor RO4987655. Among 12 patients with melanoma BRAF wild type and non-NRAS or NRAS unknown status, seven patients experienced partial response or stable disease.	Melanoma	Sensitivity/Response

DEL 485-490 (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: D Status: accepted Direction: Supports Cells harboring in-frame deletions in BRAF in the L485-P490 amino acid region were found to be sensitive to the RAF dimer inhibitor LY3009120, but not sensitive to the BRAF-selective inhibitors vemurafenib or dabrafenib. These deletions were observed in KRAS wildtype pancreatic, ovarian, NSCLC, and thyroid cancers. In three cell lines H2405 (NSCLC with L485-P490>Y), BxPC-3 (pancreatic with V487-P492>A), and OV-90 (ovarian with N486-P490del), BRAF deletion–mediated MAPK activation was found to be sensitive to LY3009120 as evidenced by dose-dependent inhibition of phospho-MEK and ERK and cell growth inhibition with IC50 values of 0.04, 0.087, and 0.007 µmol/L in these three cell lines. LY3009120, but not vemurafenib, also inhibited tumor growth of both H2405 and BxPC-3 cells xenografted into mice.	Cancer	Sensitivity/Response
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: B Status: accepted Direction: Does Not Support A quantitative synthesis was performed on nine studies comparing treatment of metastatic colorectal cancer with cetuximab or panitumumab and chemotherapy, versus chemotherapy alone, or with other targeted inhibitors. It was found that in the patient subgroup with BRAF mutation (V600E in the majority of cases), there were no benefits to overall survival, progression free survival, or overall response rate with addition of cetuximab or panitumumab to treatment. This conclusion held in the first line treatment as well as general treatment setting.	Colorectal Cancer	Sensitivity/Response
TRIM24-BRAF *Representative Transcript:* ENST00000343526.4 *Rating:* 3	**Predictive** Level: D Status: accepted Direction: Supports Foundation One NGS assay and targeted RNAseq identified PAPSS1-BRAF fusion in a melanoma sample. Further BRAF fusions (TRIM24-BRAF) were identified in TCGA and additional samples. Ectopic expression of engineered cDNA in 293H cells showed that trametinib led to reduced ERK1/2 phosphorylation in fusion positive cells whereas vemurafenib was not effective.	Skin Melanoma	Resistance
PPFIBP2-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000299492.4 *Rating:* 2	**Predictive** Level: C Status: accepted Direction: Supports Case report of a 47year old female patient with metastatic melanoma (BRAF, NRAS, KIT negative). A PPFIBP2-BRAF fusion was identified from DNA from a brain metastasis (inton 3 of PPFIBP2 fused to intron 10 of BRAF). Trametinib was introduced and anemia and ECOG status improved. Imaging revealed a 90% decrease in extracranial and 19% decrease in intracranial metastases with no new metastases and no progressing sites at 6 weeks. Trametinib was stopped and pembrolizumab introduced at this time. Progressive disease was noted after 5 cycles of pembrolizumab but re-introduction of trametinib did not show an effect.	Skin Melanoma	Sensitivity/Response
KIAA1549-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000440172.1 *Rating:* 1	**Predictive** Level: C Status: accepted Direction: Supports A 65 yr old male patient with metastatic acral lentiginous melanoma (BRAF, NRAS, KIT negative) was found to harbor a KIAA1549-BRAF (intron 15-intron 8) fusion in a subcutaneous metastasis sample after disease progression. Trametinib was started and fatigue and ECOG status improved but imaging revealed slight disease progression after 2 weeks (15 sites measurable, 9 stable, 6 progressive). No new metastases were identified. The patient was switched to pembrolizumab and major disease progression was noted.	Skin Melanoma	Sensitivity/Response

BRAF-CUL1 (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 2	**Predictive** Level: C Status: accepted Direction: Supports One patient with low-grade serous ovarian cancer had an in-frame fusion between the BRAF kinase domain and CUL1 identified by panel sequencing (MSK-IMPACT), with expression confirmed by whole-transcriptome sequencing. This patient with metastatic disease after treatment with carboplatin and paclitaxel, was enrolled onto a study of paclitaxel in combination with an oral MEK inhibitor and achieved a CR. She continued to receive therapy for 7 months, until discontinuation because of the development of pneumonitis. At publication, sustained CR had lasted > 18 months.	Ovarian Serous Carcinoma	Sensitivity/Response
ZKSCAN1-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000426572.1 *Rating:* 3	**Predictive** Level: C Status: accepted Direction: Supports Analysis of BRAF fusions in 20,573 tumors, across 12 distinct tumor types. BRAF fusions were identified in 55 (0.3%) patients and enriched in spitzoid melanoma, pilocytic astrocytomas, pancreatic acinar and papillary thyroid cancers. Clinical data were available for two patients. Among them one 46-year old woman with spitzoid melanoma that harbored a ZKSCAN1-BRAF fusion responded to treatment with the MEK inhibitor trametinib. Subcutaneous tumor nodules exhibited clinical responses within 14 days of therapy, and her dominant bulky right lung metastases showed significant response by Day 45. Subsequent robotic-assisted lobectomy was able to remove the previously unresectable tumor with clean surgical margins.	Melanoma	Sensitivity/Response
KIAA1549-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000440172.1 *Rating:* 2	**Predictive** Level: C Status: accepted Direction: Supports A patient with a malignant spindle cell tumor of the chest wall treated as a soft tissue sarcoma was identified to harbor a KIAA1549-BRAF fusion. This patient responded to treatment with the pan-kinase inhibitor sorafenib in combination with bevacizumab and temsirolimus, achieving stable disease after 2 cycles extending into 11 cycles at which time she expired due to co-morbidities (acute myocardial infarction, hypotension). Of note, sequencing of 236 cancer-related genes identified CDKN2A A68fs*51, SUFU E283fs*3, MAP3K1 N325fs*3 and homozygous deletion of PTEN as well.	Sarcoma	Sensitivity/Response
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 2	**Predictive** Level: D Status: accepted Direction: Supports A cohort of patient-derived xenografts (PDX) from 85 patients with metastatic colorectal cancer was created. PDX were treated with cetuximab and mechanisms of resistance investigated. None of the xenografts harboring KRAS (N=18), NRAS (N=7) or BRAF (N=3) mutations showed a response to cetuximab whereas 1 out of 4 xenografts with a PIK3CA mutation responded to cetuximab.	Colorectal Cancer	Resistance
AMPLIFICATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: C Status: accepted Direction: Supports Paired pre-treatment and post-progression tumor biopsies from BRAF-mutant CRC patients treated with RAF inhibitor combinations were analyzed. Alterations in MAPK pathway genes were found in resistant tumors not present in matched pre-treatment tumors, including KRAS amplification, BRAF amplification, and a MEK1 mutation.	Colorectal Cancer	Resistance

MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Prognostic** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 168 metastatic colorectal cancer patients who received first line chemotherapy (made up of 5-fluorouracil (5-FU) only, 5-FU + oxaliplatin, 5-FU + irinotecan, or 5-FU + oxaliplatin + irinotecan) alone or with monoclonal antibodies (bevacizumab or cetuximab). It assessed the relationship between BRAF mutation status in primary tumors and post treatment PFS. Of 168 patients, 155 had wildtype BRAF and 13 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation had a significantly worse outcome than patients expressing wildtype BRAF, regardless of first line chemotherapy regimen or use of monoclonal antibody treatment (Median PFS: 4.3 and 12.5 months, respectively; p <.0001).	Colorectal Cancer	Poor Outcome
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 100 metastatic colorectal cancer patients who received FOLFOX (oxaliplatin + 5-fluorouracil + folinic acid) first-line therapy alone or with monoclonal antibodies (bevacizumab or cetuximab). It assessed the relationship between BRAF mutation status in primary tumors and response to oxaliplatin-based first-line therapy, as measured by post treatment PFS. Of 100 patients, 94 had wildtype BRAF and 6 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation were significantly more resistant to oxaliplatin-based first-line therapy than patients with wildtype BRAF (Median PFS: 5.0 and 11. 7 months, respectively; p < .0001).	Colorectal Cancer	Resistance
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 44 metastatic colorectal cancer patients who received FOLFIRI (5-Fluorouacil + Folinic acid + irinotecan) first-line therapy alone or with bevacizumab. It assessed the relationship between BRAF mutation status in primary tumors and response to irinotecan-based first line therapy, as measured by PFS. Of the 44 patients, 39 had wildtype BRAF and 5 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation were significantly more resistant to irinotecan-based first-line therapy than patients with wildtype BRAF (Median PFS: 3.5 and 12.8 months, respectively; p = .006).	Colorectal Cancer	Resistance
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 97 metastatic colorectal cancer patients who received bevacizumab in conjunction with first-line chemotherapy (composed of 5-fluorouracil (5-FU) only, 5-FU + oxaliplatin, 5-FU + irinotecan, or 5-FU + oxaliplatin + irinotecan). It assessed the relationship between BRAF mutation status in primary tumors and response to bevacizumab-containing first line chemotherapy, as measured by PFS. Of the 97 patients,89 had wildtype BRAF and 8 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation were significantly more resistant to bevacizumab-containing first-line chemotherapy than patients with wildtype BRAF (Median PFS: 4.2 and 12.5 months, respectively; p < .0001).	Colorectal Cancer	Resistance

MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Predictive** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 92 metastatic colorectal cancer patients who received cetuximab in conjunction with salvage chemotherapy (refractory to at least one line of treatment). Salvage chemotherapy was composed of 5-fluorouracil (5-FU) only, 5-FU + oxaliplatin, 5-FU + irinotecan, or 5-FU + oxaliplatin + irinotecan. The study assessed the relationship between BRAF mutation status in primary tumors and response to cetuximab-containing salvage chemotherapy, as measured by PFS. Of the 92 patients, 83 had wildtype BRAF and 9 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation were significantly more resistant to cetuximab-containing salvage chemotherapy than patients with wildtype BRAF (Median PFS: 2.0 and 3.9, respectively; p = .0005).	Colorectal Cancer	Resistance
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 3	**Prognostic** Level: B Status: accepted Direction: Supports This was a retrospective clinical study of 168 metastatic colorectal cancer patients who received first line chemotherapy (made up of 5-fluorouracil (5-FU) only, 5-FU + oxaliplatin, 5-FU + irinotecan, or 5-FU + oxaliplatin + irinotecan) alone or with monoclonal antibodies (bevacizumab or cetuximab). It assessed the relationship between BRAF mutation status in primary tumors and post treatment OS. Of 168 patients, 155 had wildtype BRAF and 13 had mutations in BRAF—including V600E and D594K. The study found that patients harboring a BRAF mutation had a significantly worse outcome than patients expressing wildtype BRAF, regardless of first line chemotherapy regimen or use of monoclonal antibody treatment (Median OS: 10.9 and 40.5 months, respectively; p <.0001).	Colorectal Cancer	Poor Outcome
KIAA1549-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000440172.1 *Rating:* 5	**Diagnostic** Level: B Status: accepted Direction: Supports Genetic alterations in pilocytic astrocytoma (PA) were evaluated. Whole-genome sequencing of normal (blood) and tumor samples (n=96) was performed along with corresponding RNA-Seq (n=73) and mate-pair (MP) sequencing (n=68). Several known events activating the MAPK pathway were identified with KIAA1549-BRAF fusion being the most frequent variants (70 of 96 cases, 73%). Importantly, all but one of the cerebellar PA harbored a BRAF fusion (47 of 48 samples, 98%) with this one exception having a KRAS alteration.	Pilocytic Astrocytoma	Positive
MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 4	**Prognostic** Level: B Status: accepted Direction: Supports In the Medical Research Council (MRC) COIN trial, ISRCTN27286448, patients who presented with advanced colorectal cancer were randomly assigned to chemotherapy (oxaliplatin and fluoropyrimidine; arm A), or chemotherapy plus cetuximab (arm B). Median overall survival was found to differ by mutation, regardless of treatment. Median overall survival was 8.8 months (IQR 4.5-27) for patients with BRAF variants, 14.4 months (IQR 8.5-24.0) for patients with KRAS variants, and 20.1 months (IQR 11.5-31.7) for wildtype patients. BRAF mutations were found in 102/1291 samples (7.90%), and of these, 12 were D594G and 90 V600E.	Colorectal Cancer	Poor Outcome

MUTATION (Somatic Mutation) *Representative Transcript:* ENST00000288602.6 *Rating:* 4	**Prognostic** Level: B Status: accepted Direction: Supports A meta analysis was performed using data from 21 published studies (n = 9885 patients) to assess prognostic value of BRAF mutations in colorectal cancer. When evaluating 14 studies (n = 7778 patients), the odds ratio (OR) of a proximal lesion, which is associated with greater mortality in colon cancer, was increased for patients with BRAF mutations (OR 5.222, 95% CI 3.801–7.174, P < 0.001). When evaluating 4 studies (n = 1526 patients), the odds ratio of T4 tumors, which indicates tumor growth past bowel lining, was increased for patients with BRAF mutations (OR 1.761, 95% CI 1.164–2.663, P = 0.007). When evaluating 8 studies (n = 2786 patients), the odds ratio of poor tumor differentiation was increased in patients with BRAF mutations (OR 3.816, 95% CI 2.714–5.365, P < 0.001). These results support that BRAF mutations indicate poor prognosis for patients with colorectal cancer.	Colorectal Cancer	Poor Outcome
KIAA1549-BRAF (Somatic Mutation) *Representative Transcript:* ENST00000440172.1 *Rating:* 3	**Functional** Level: D Status: accepted Direction: Supports This study identified a novel rearrangement event between the uncharacterized gene KIAA-1549 and BRAF in 66% (29 of 44) of pilocytic astrocytoma. The fusion gene was shown to delete the N-terminal BRAF auto-regulatory domain which in vitro assays indicated leads to constitutive activation of BRAF. Cos7 cells were transfected with two isoforms of KIAA1549-BRAF (both exon 16:exon 9), BRAF V600E, or wildtype BRAF and evaluated activity via BRAF kinase assay. Both fusion isoforms showed similar or higher kinase activity than V600E transfected cells. NIH3T3 cells transfected with V600E or the short fusion isoform also demonstrated anchorage-independent growth in soft agarose.	Pilocytic Astrocytoma	Gain of Function

BRAF V600D, BRAF V600E, BRAF V600K, BRAF V600R, BRAF codon(s) 600 any, BRAF any mutation

B-RAF is a member of the RAF-family of kinases which plays an important role in the RAS-RAF-MEK-ERK mitotic signaling pathway. Mutations of B-RAF have been described in up to 100% of Hairy cell leukemia, 40-70% of Langerhans cell histiocytosis, approximately 50% of Erdheim-Chester disease, approximately 5% of diffuse large B cell lymphoma and plasma cell neoplasms and less than 5% of chronic lymphocytic leukemia. While some reports have found that 10-20% of cases of acute leukemias (ALL or AML) may have BRAF mutations, other reports have described no BRAF in those diseases or in myeloid diseases such as MDS or CML. The hotspot for mutations in BRAF is at codon Val600 and these are activating mutations. The most common activating mutation is p.Val600Glu(V600E). Various B-Raf inhibitors(Vemurafenib, Dabrafenib) have been FDA approved for therapy for some tumor types in certain clinical settings.

Tumor	Tissue
Acute Myeloid Leukemia, Atypical Chronic Myeloid Leukemia, B Lymphoblastic Leukemia/Lymphoma, Chronic Lymphocytic Leukemia, Chronic Myeloid Leukemia, Chronic Myelomonocytic Leukemia, Chronic Neutrophilic Leukemia, Diffuse Large B Cell Lymphoma, Essential Thrombocythemia, Mast Cell Neoplasm, MDS with Ring Sideroblasts, Myelodysplastic Syndrome, Myeloproliferative Neoplasm, Polycythemia Vera, Primary Myelofibrosis, T Lymphoblastic Leukemia/Lymphoma, Leukocytosis, Thrombocytosis, Monocytosis, Cytopenia, Other Acute Leukemia, Acute Leukemia of Unspecified Cell Type, Anemia, Unspecified, Leukopenia, Thrombocytopenia, Eosinophilia, Myelodysplastic/Myeloproliferative Neoplasm, Myeloid Neoplasm, Polycythemia	Blood, Bone Marrow

> ***Incidence of the BRAF V600E mutation in chronic lymphocytic leukaemia and prolymphocytic leukaemia.***
>
> Langabeer, SE, Quinn, F, O'Brien, D, McElligott, AM, Kelly, J, Browne, PV, Vandenberghe, E **Leukemia research**

> ***Absence of BRAF V600E mutation in hematologic malignancies excluding hairy-cell leukemia.***
>
> Ping, N, Wang, Q, Wang, Q, Dong, S, Wu, L, Xue, Y, Ruan, C, Wu, D, Chen, S **Leukemia & lymphoma**

> ***BRAF V600E mutation in adult acute lymphoblastic leukemia.***
>
> Alonso, CM, Such, E, Gómez-Seguí, I, Cervera, J, Martínez-Cuadrón, D, Luna, I, Ibáñez, M, López-Pavía, M, Vera, B, Navarro, I, Senent, L, Sanz Alonso, MA **Leukemia & lymphoma**

BRAF mutations in chronic lymphocytic leukemia.

Jebaraj, BM, Kienle, D, Bühler, A, Winkler, D, Döhner, H, Stilgenbauer, S, Zenz, T **Leukemia & lymphoma**

Efficacy of vemurafenib in hairy-cell leukemia.

Samuel, J, Macip, S, Dyer, MJ **The New England journal of medicine**

Clinical Trials

Title	Conditions	Phenotypes	Status	Source
A Phase Ib Study Combining Irinotecan With AZD1775, a Selective Wee 1 Inhibitor, in RAS (KRAS or NRAS) or BRAF Mutated Metastatic Colorectal Cancer Patients Who Have Progressed on First Line Therapy	Metastatic Colorectal Cancer		Recruiting	NYU Langone Health
A Phase Ib, Open-Label Study of The Safety and Pharmacology of Atezolizumab (Anti PD-L1 Antibody) Administered in Combination With Vemurafenib or Vemurafenib Plus Cobimetinib in Patients With BRAFV600-Mutation Positive Metastatic Melanoma	Malignant Melanoma		Active, not recruiting	Genentech, Inc.
Retrospective Study Assessing Molecular Features Predicting Response or Resistance to Cetuximab Therapy in Metastatic Colorectal Cancer Patients	Colorectal Neoplasms		Completed	Istituto Clinico Humanitas
A Four-Part, Open-Label Study to Evaluate the Effects of Repeat Dose GSK2118436 on the Single Dose Pharmacokinetics of Warfarin, the Effects of Repeat Dose Oral Ketoconazole and Oral Gemfibrozil on the Repeat Dose Pharmacokinetics of GSK2118436, and the Repeat Dose Pharmacokinetics of GSK2118436 in Subjects With BRAF Mutant Solid Tumors	Cancer	oncology	Completed	GlaxoSmithKline
"A Phase I/II Dose-Escalation Study Evaluating the Combination of Neratinib and Cetuximab in Patients With Quadruple Wild-Type (KRAS/NRAS/BRAF/PIK3CA Wild-Type) Metastatic Colorectal Cancer Resistant to Cetuximab"	Colorectal Cancer		Withdrawn	NSABP Foundation Inc
Cetuximab Monotherapy and Cetuximab Plus Capecitabine as First-line Treatment in Elderly Patients With KRAS- and BRAF Wild-type Metastatic Colorectal Cancer. A Multicenter Phase II Trial	Metastatic Colorectal Cancer		Terminated	Swiss Group for Clinical Cancer Research
The Prospective Non-randomized Phase II Clinical Trial of Vemurafenib in Combination With Cytarabine and 2-chlorodeoxyadenosine in Children With Langerhans-cell Hisitocytosis With BRAF V600E Mutation	Langerhans Cell Histiocytosis, histiocytosis		Recruiting	Federal Research Institute of Pediatric Hematology, Oncology and Immunology
An Open-label, Dose Escalation, Phase I Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of GSK2118436 in Japanese Subjects With BRAF V600 Mutation Positive Solid Tumors	Cancer		Completed	GlaxoSmithKline
A Phase II Study of First-Line Chemotherapy and Panitumumab in Advanced NSCLC Selected by Mutational Status	Non Small Cell Lung Cancer, Lung Cancer		Terminated	Vejle Hospital

A Pilot Study of Dabrafenib and Trametinib for Patients With BRAF Mutated Ameloblastoma	Ameloblastoma, BRAF Gene Mutation, adamantinoma		Active, not recruiting	Stanford University
A Phase 1 Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	Advanced Cancer, Metastatic Melanoma, Metastatic Non-small Cell Lung Cancer, Metastatic Pancreatic Ductal Adenocarcinoma, Colorectal Cancer		Recruiting	Eli Lilly and Company
A Phase 1 First-in-Human Study of KO-947 in Locally Advanced Unresectable or Metastatic, Relapsed and/or Refractory Non-Hematological Malignancies	Advanced Malignant Neoplasm		Recruiting	Kura Oncology, Inc.
A Randomized Phase 2 Study of Single Agent Dabrafenib (BRAFi) vs. Combination Regimen Dabrafenib (BRAFi) and Trametinib (MEKi) in Patients With BRAF Mutated Thyroid Carcinoma	Follicular Thyroid Cancer, Insular Thyroid Cancer, Papillary Thyroid Cancer, Recurrent Thyroid Cancer, thyroid cancer, thyroid carcinoma		Active, not recruiting	Ohio State University Comprehensive Cancer Center
The Oncopanel Pilot (TOP) Study	Colorectal Cancer Metastatic, Advanced Non-Small Cell Lung Carcinoma, Advanced Melanoma, Gastrointestinal Stromal Tumors, Patients With Diagnosed Malignancies Being Considered for Clinical Trials		Completed	British Columbia Cancer Agency
French National Observatory of the Patients With Non-small Cell Lung (NSCLC) Benefiting From a Molecular Test on the Hospital Platforms of Molecular Genetics.	Carcinoma, Non-Small-Cell Lung, ALK Gene Mutation, KRAS Gene Mutation, BRAF Gene Mutation, lung cancer		Completed	Intergroupe Francophone de Cancerologie Thoracique
Randomised Study to Investigate FOLFOXIRI Plus Cetuximab vs. FOLFOXIRI Plus Bevacizumab as First-line Treatment of BRAF-mutated Metastatic Colorectal Cancer	Metastatic Colorectal Cancer		Recruiting	Ludwig-Maximilians - University of Munich
Phase II Biomarker Study Evaluating The Upfront Combination Of BRAF Inhibitor Dabrafenib With MEK Inhibitor Trametinib Versus The Combination After Eight Weeks Of Monotherapy With Dabrafenib Or Trametinib In Patients With Metastatic And Unresectable Stage III Or IV Melanoma Harbouring An Activating BRAF Mutation	Melanoma	Oncology	Terminated	GlaxoSmithKline
Phase II Clinical Trial of the MEK Inhibitor Trametinib With the AKT Inhibitor GSK2141795 in BRAF Wild-type Melanoma	Melanoma		Unknown status	University of California, San Francisco
A Phase II Study of the BRAF Inhibitor, Vemurafenib, Plus Obinutuzumab in Patients With Previously Untreated Classical Hairy Cell Leukemia	Hairy Cell Leukemia, Leukemia, Leukemia, Hairy Cell		Recruiting	Memorial Sloan Kettering Cancer Center
A Multicenter, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA) /Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With BRAF V600E-mutant Metastatic Colorectal Cancer	BRAF V600E-mutant Metastatic Colorectal Cancer, Colorectal cancer		Active, not recruiting	Array BioPharma

A Phase 1/2 Trial of BKM120 Combined With Vemurafenib (PLX4032) in BRAFV600E/K Mutant Advanced Melanoma (Novartis Study Number CBKM120ZUS21T)	BRAF Mutant Metastatic Melanoma, Melanoma		Completed	University of California, San Francisco
"A Phase II Study Evaluating the Combination of Neratinib Plus Trastuzumab or Neratinib Plus Cetuximab in Patients With Quadruple Wild-Type (KRAS/NRAS/BRAF/PIK3CA Wild-Type) Metastatic Colorectal Cancer Based on HER2 Status: Amplified, Non-Amplified (Wild-Type) or Mutated"	Metastatic Colorectal Cancer		Recruiting	NSABP Foundation Inc
A Randomized Phase 2 Pilot Study of Type I-Polarized Autologous Dendritic Cell Vaccines Incorporating Tumor Blood Vessel Antigen (TBVA)-Derived Peptides in Combination With Dasatinib in Patients With Metastatic Melanoma	Metastatic Melanoma, melanoma		Completed	University of Pittsburgh
An Open-Label, Dose-Finding and Proof of Concept Study of the PD-L1 Probody™ Therapeutic , CX-072, as Monotherapy and in Combination With Yervoy (Ipilimumab) or With Zelboraf (Vemurafenib) in Subjects With Advanced or Recurrent Solid Tumors or Lymphomas	Solid Tumor, Lymphoma, cancer		Recruiting	CytomX Therapeutics
Phase I Study of Escalating Doses of XL888 With Vemurafenib for Patients With Unresectable BRAF Mutated Stage III/IV Melanoma	Melanoma, skin cancer		Active, not recruiting	H. Lee Moffitt Cancer Center and Research Institute
Phase I Trial of Phenformin With Dabrafenib and Trametinib in Patients With BRAFV600E/K-mutated Melanoma	Melanoma		Recruiting	Memorial Sloan Kettering Cancer Center
A Phase Ib/II, Multicenter, Study of LEE011 in Combination With LGX818 in Adult Patients With BRAF Mutant Melanoma.	Locally Advanced Metastatic BRAF Mutant Melanoma, Metastatic melanoma		Terminated	Array BioPharma
A Phase Ib, Open-label, Multicenter Study of Oral LXH254-centric Combinations in Adult Patients With Advanced or Metastatic KRAS or BRAF Mutant Non-Small Cell Lung Cancer or NRAS Mutant Melanoma	Non-Small Cell Lung Cancer, Melanoma, lung cancer, lung adenocarcinoma, Large-cell lung carcinoma, squamous cell lung carcinoma		Recruiting	Novartis
Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced BRAF V600-Mutation Positive Solid Tumors	Neoplasms, Brain		Active, not recruiting	Novartis
Immune Modulation Study in Patients With Metastatic Melanoma Treated With Anti-PD1 Monoclonal Antibodies	Metastatic Melanoma, Melanoma		Unknown status	Hospices Civils de Lyon
A Japanese Open-label Phase I/II Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of GSK2118436 and GSK1120212 Combination Therapy in Subjects With BRAF V600E/K Mutation Positive Advanced Solid Tumors (Phase I Part) and BRAF V600E/K Mutation Positive Cutaneous Melanoma (Phase II Part).	Solid Tumours, Melanoma		Completed	GlaxoSmithKline
Exploring the Utility of a Novel BRAF Test in Patients With Melanoma	Melanoma		Active, not recruiting	Massachusetts General Hospital

A Phase II, Randomised, Open Label Study of Neoadjuvant Dabrafenib, Trametinib and / or Pembrolizumab in BRAF V600 Mutant Resectable Stage IIIB/C Melanoma	Melanoma		Recruiting	Melanoma Institute Australia
A Phase Ib/II Open-label, Multi-center Study of the Combination of MEK162 Plus AMG 479 (Ganitumab) in Adult Patients With Selected Advanced Solid Tumors	Metastatic Pancreatic Adenocarcinoma, BRAF Mutated Melanoma, colorectal adenocarcinoma, pancreatic adenocarcinoma, melanoma		Terminated	Array BioPharma
A Phase I Trial of MEK Inhibitor Trametinib in Combination With Neoadjuvant 5-Fluorouracil Chemoradiation in the Treatment of KRAS, BRAF, and NRAS-MUTANT Rectal Cancers	Recurrent Rectal Cancer, Stage IIA Rectal Cancer, Stage IIB Rectal Cancer, Stage IIC Rectal Cancer, Stage IIIA Rectal Cancer, Stage IIIB Rectal Cancer, Stage IIIC Rectal Cancer		Active, not recruiting	Ohio State University Comprehensive Cancer Center
Phase II, Multi-center, Open-label Study of Single-agent LGX818 Followed by a Rational Combination With Agents After Progression on LGX818, in Adult Patients With Locally Advanced or Metastatic BRAF V600 Melanoma	Melanoma, metastatic melanoma		Terminated	Array BioPharma
A Phase II, Open-label, Multicenter, Randomized Study to Assess the Efficacy and Safety of GSK1120212 Compared With Docetaxel in 2nd Line Subjects With Targeted Mutations (KRAS, NRAS, BRAF, MEK1) in Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC Stage IV)	Lung Cancer, Non-Small Cell		Completed	GlaxoSmithKline
Impact of BRAFV600E Intratumor Heterogeneity on the Efficacy of Tyrosine Kinase Inhibitors in the Treatment of Radioiodine-resistant Thyroid Cancer	Differentiated Thyroid Cancer, thyroid cancer		Unknown status	University of Salerno

Drug related

BRAF related drugs

Drug name	Attributes	Disease

Plx-4720 Interaction type: inhibitor Approved: No	*Drug Family*: BRAF inhibitor *Alteration*: BRAF:V600E *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True *Direct Interaction*: False *Response Type*: resistant *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Approval Status*: Preclinical *Response Type*: predicted – resistant *Response Type*: decreased response *Combination Therapy*: PLX4720 + Tivozanib *Response Type*: sensitive *Combination Therapy*: PLX4720 + Doxorubicin *Combination Therapy*: Cediranib + Selumetinib + PLX4720 *Combination Therapy*: Cediranib + PLX4720 *Combination Therapy*: PLX4720 + Navitoclax *Combination Therapy*: Erlotinib + PLX4720 *Combination Therapy*: PLX4720 + TAK-632 *Combination Therapy*: Imatinib + PLX4720 *Combination Therapy*: Gefitinib + PLX4720 *Combination Therapy*: Everolimus + PLX4720 *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Cell culture *Combination Therapy*: Alpelisib + PLX4720 *Combination Therapy*: BI2536 + PLX4720 *Combination Therapy*: Selumetinib + PLX4720 *Combination Therapy*: PLX4720 + Vorinostat *Combination Therapy*: Cetuximab + PLX4720 *Combination Therapy*: GDC-0941 + PLX4720	Advanced Solid Tumor, Colon Cancer, Colorectal Cancer, Glioblastoma Multiforme, Malignant Glioma, Melanoma
Cep-32496 Interaction type: inhibitor Approved: No	*Details Of The Assay For Interaction*: Inhibition of wild type BRAF activity. *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Colon Carcinoma, Melanoma

Trametinib Approved: Yes	*Combination Therapy*: Dabrafenib;Trametinib *Drug Family*: BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E *Combination Therapy*: Panitumumab;Dabrafenib;Trametinib *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E,V600K *Drug Family*: MEK inhibitor *Drug Family*: [MEK inhibitor] *Alteration*: BRAF:K601R,L597R,V600R *Alteration*: BRAF__. *Combination Therapy*: Trametinib + Dabrafenib *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Approval Status*: Preclinical *Combination Therapy*: Palbociclib + Trametinib *Response Type*: decreased response *Approval Status*: Phase I *Combination Therapy*: Dabrafenib + Everolimus + Trametinib *Approval Status*: Clinical Study *Response Type*: resistant *Combination Therapy*: Cetuximab + Dabrafenib + Trametinib *Combination Therapy*: Trametinib + TW-37 *Combination Therapy*: Trametinib + Navitoclax *Combination Therapy*: PAC-1 + Trametinib + Vemurafenib *Approval Status*: Phase II *Approval Status*: Guideline *Combination Therapy*: Dasatinib + Trametinib *Combination Therapy*: Trametinib + Vemurafenib *Approval Status*: FDA approved *Combination Therapy*: BI 882370 + Trametinib *Response Type*: predicted – sensitive *Combination Therapy*: GSK2126458 + Trametinib *Combination Therapy*: ARQ092 + Trametinib *Approval Status*: Preclinical - Pdx *Response Type*: no benefit *Approval Status*: Phase III *Combination Therapy*: INC280 + Trametinib *Combination Therapy*: S63845 + Trametinib *Combination Therapy*: Panitumumab + Trametinib + Dabrafenib *Approval Status*: Phase Ib/II *Combination Therapy*: MK2206 + Trametinib *Combination Therapy*: AMG 232 + Trametinib + Dabrafenib *Combination Therapy*: BKM120 + Trametinib *Combination Therapy*: Dabrafenib + Trametinib *Clinical Status*: FDA-approved *Pathway*: activation *Variant Effect*: gain-of-function *Clinical Status*: case report	Advanced Solid Tumor, Collecting Duct Carcinoma, Colon Cancer, Colorectal Cancer, Lung Adenocarcinoma, Lung Cancer, Melanoma, Multiple Myeloma, Neuroendocrine Tumor, Non-Small Cell Lung Carcinoma, Ovarian Cancer, Pancreatic Adenocarcinoma, Pancreatic Cancer, Pilocytic Astrocytoma, Thyroid Cancer, Thyroid Carcinoma, Triple-Receptor Negative Breast Cancer
Pembrolizumab Approved: Yes	*Response Type*: no benefit *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: GSK2636771 + Pembrolizumab *Response Type*: sensitive	Melanoma

Irinotecan Approved: Yes	*Combination Therapy*: Cetuximab + Irinotecan *Response Type*: resistant *Approval Status*: Clinical Study *Evidence Type*: Actionable *Combination Therapy*: Irinotecan + Panitumumab *Response Type*: predicted – sensitive *Combination Therapy*: Vemurafenib + Cetuximab + Irinotecan *Response Type*: sensitive *Approval Status*: Phase Ib/II	Colorectal Cancer
Phenmetrazine Approved: Yes	*Response Type*: no benefit *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma
Panobinostat Approved: Yes	*Combination Therapy*: Lapatinib + Panobinostat *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Colorectal Cancer
Vemurafenib Interaction type: inhibitor Approved: Yes	*Trial Name*: PLX4032, RG7204 *Novel Drug Target*: Established target *Drug Family*: BRAF inhibitor *Alteration*: BRAF:V600D,V600K,V600M,V600G,V600R *Alteration*: BRAF:V600E *Combination Therapy*: Vemurafenib;Cobimetinib *Drug Family*: BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E,V600K *Alteration*: BRAF:V600. *Alteration*: BRAF:V600E,V600D,V600K,V600M,V600G,V600R *Combination Therapy*: Vemurafenib;Panitumumab *Drug Family*: BRAF inhibitor;EGFR mAb inhibitor *Alteration*: MET:amp;BRAF:V600E *Combination Therapy*: Crizotinib;Vemurafenib *Drug Family*: ALK inhibitor;BRAF inhibitor *Alteration*: NF1:del;BRAF:. *Alteration*: NF1:.;BRAF:. *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True *Combination Therapy*: Vemurafenib + Panitumumab *Combination Therapy*: Vemurafenib + Cetuximab *Combination Therapy*: Vemurafenib + Cobimetinib *Notes*: V600E mutation *Response Type*: resistant *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Approval Status*: Preclinical *Response Type*: sensitive *Approval Status*: Clinical Study *Response Type*: decreased response *Approval Status*: Phase II *Approval Status*: Guideline *Approval Status*: FDA approved *Combination Therapy*: Vemurafenib + TW-37 *Combination Therapy*: PAC-1 + Trametinib + Vemurafenib *Approval Status*: Phase I *Combination Therapy*: Lapatinib + Vemurafenib *Combination Therapy*: Vemurafenib + Gefitinib *Combination Therapy*: Navitoclax + Vemurafenib *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Trametinib + Vemurafenib *Response Type*: no benefit *Combination Therapy*: Vemurafenib + SBI-060756 *Combination Therapy*: Vemurafenib + Erlotinib *Combination Therapy*: DETD-35 + Vemurafenib	Advanced Solid Tumor, Cholangiocarcinoma, Colon Cancer, Colorectal Cancer, Hairy Cell Leukemia, Lung Adenocarcinoma, Melanoma, Neuroendocrine Tumor, Non-Small Cell Lung Carcinoma, Ovarian Cancer, Pancreatic Cancer, Renal Cell Carcinoma, Thyroid Cancer

	Combination Therapy: PAC-1 + Vemurafenib *Combination Therapy*: PLX3397 + Vemurafenib *Combination Therapy*: Selumetinib + Vemurafenib *Combination Therapy*: Cetuximab + Selumetinib + Vemurafenib *Combination Therapy*: BEZ235 + Vemurafenib *Combination Therapy*: Vemurafenib + ZSTK474 *Approval Status*: Preclinical - Pdx *Response Type*: conflicting *Combination Therapy*: S63845 + Vemurafenib *Combination Therapy*: Vemurafenib + Voruciclib *Combination Therapy*: PET-16 + Vemurafenib *Combination Therapy*: SAR260301 + Vemurafenib *Combination Therapy*: Vemurafenib + Cetuximab + Irinotecan *Approval Status*: Phase Ib/II *Combination Therapy*: BKM120 + Vemurafenib *Combination Therapy*: Atezolizumab + Vemurafenib + Cobimetinib *Combination Therapy*: MK2206 + Vemurafenib *Response Type*: predicted – sensitive *Response Type*: predicted – resistant *Clinical Status*: FDA-approved *Pathway*: activation *Variant Effect*: gain-of-function *Clinical Status*: case report *Clinical Status*: early trials *Clinical Status*: late trials	
Lenvatinib Approved: Yes	*Response Type*: sensitive *Approval Status*: Phase I *Evidence Type*: Actionable	Melanoma
Voruciclib Approved: No	*Combination Therapy*: Vemurafenib + Voruciclib *Response Type*: sensitive *Approval Status*: Phase I *Evidence Type*: Actionable	Melanoma
Tubastatin A Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma
Gedatolisib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Breast Cancer, Colon Cancer
XI-281 Interaction type: inhibitor Approved: No	*Trial Name*: XL281 *Novel Drug Target*: Established target *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	
Uprosertib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable	Melanoma
Bevacizumab Approved: Yes	*Combination Therapy*: Bevacizumab + Temsirolimus + Doxil *Response Type*: sensitive *Approval Status*: Clinical Study *Evidence Type*: Actionable	Ovarian Carcinoma
Afatinib Approved: Yes	*Combination Therapy*: BI 882370 + Afatinib *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Colorectal Cancer

Temsirolimus Interaction type: inhibitor Approved: Yes	*Combination Therapy*: Bevacizumab + Temsirolimus + Doxil *Response Type*: sensitive *Approval Status*: Clinical Study *Evidence Type*: Actionable *Combination Therapy*: Sorafenib + Temsirolimus	Ovarian Carcinoma
Zstk-474 Approved: No	*Combination Therapy*: Vemurafenib + ZSTK474 *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Selumetinib + ZSTK474 *Approval Status*: Preclinical - Cell line xenograft	Melanoma
Tivozanib Approved: No	*Combination Therapy*: PLX4720 + Tivozanib *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma
Pictilisib Approved: No	*Combination Therapy*: GDC0879 + GDC-0941 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: GDC-0941 + PLX4720 *Approval Status*: Preclinical *Combination Therapy*: GDC-0941 + Binimetinib *Combination Therapy*: GDC-0941 + NVP-AEW541 *Combination Therapy*: GDC-0941 + LGX818	Melanoma
Sb590885 Interaction type: inhibitor Approved: No	*Details Of The Assay For Interaction*: In a cell-free assay *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: resistant *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: predicted – resistant *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture	Advanced Solid Tumor, Melanoma
Lgx-806 Interaction type: inhibitor Approved: No	*Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	
Ci-1040 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: resistant *Approval Status*: Preclinical - Cell line xenograft *Response Type*: predicted – sensitive	Advanced Solid Tumor, Melanoma, Ovarian Cancer
Lapatinib Approved: Yes	*Combination Therapy*: Lapatinib + Panobinostat *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Lapatinib + Vemurafenib	Colorectal Cancer, Thyroid Cancer
Chembl2204502 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma

Aew-541 Approved: No	*Combination Therapy*: AZD6482 + NVP-AEW541 *Response Type*: no benefit *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: GSK2636771 + NVP-AEW541 *Response Type*: sensitive *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + NVP-AEW541 *Combination Therapy*: AZD6482 + LGX818 + NVP-AEW541 *Combination Therapy*: GDC-0941 + NVP-AEW541 *Combination Therapy*: BYL719 + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + NVP-AEW541	Melanoma
Doxorubicin Approved: Yes	*Combination Therapy*: PLX4720 + Doxorubicin *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable	Melanoma
Pf-00477736 Approved: No	*Combination Therapy*: PF3644022 + PF-477736 *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Patient cell culture *Evidence Type*: Actionable *Approval Status*: Preclinical - Cell culture *Approval Status*: Preclinical - Cell line xenograft	Advanced Solid Tumor, Colon Cancer, Lung Adenocarcinoma
Vorinostat Approved: Yes	*Combination Therapy*: PLX4720 + Vorinostat *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable	Melanoma
Omipalisib Approved: No	*Combination Therapy*: Dabrafenib + GSK2126458 *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: GSK2126458 + Trametinib *Response Type*: decreased response *Response Type*: no benefit *Response Type*: conflicting	Melanoma
Cobimetinib Approved: Yes	*Combination Therapy*: Vemurafenib;Cobimetinib *Drug Family*: BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E,V600K *Combination Therapy*: Vemurafenib + Cobimetinib *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Combination Therapy*: Atezolizumab + Vemurafenib + Cobimetinib *Approval Status*: Phase Ib/II *Approval Status*: FDA approved	Colorectal Cancer, Melanoma
Ly-294002 Approved: No	*Combination Therapy*: E6201 + LY294002 *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma

Selumetinib Approved: No	*Combination Therapy*: Selumetinib + Paclitaxel *Drug Family*: MEK inhibitor *Alteration*: BRAF__. *Alteration*: BRAF:V600E *Alteration*: NF1:del;BRAF:. *Alteration*: NF1:.;BRAF:. *Response Type*: decreased response *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: no benefit *Approval Status*: Phase II *Combination Therapy*: Everolimus + Selumetinib *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Cell culture *Response Type*: resistant *Combination Therapy*: Cetuximab + Selumetinib *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Cediranib + Selumetinib + PLX4720 *Combination Therapy*: Selumetinib + PLX4720 *Combination Therapy*: Dasatinib + Selumetinib *Combination Therapy*: Selumetinib + Vemurafenib *Combination Therapy*: Cetuximab + Selumetinib + Vemurafenib *Combination Therapy*: Selumetinib + BEZ235 *Combination Therapy*: Selumetinib + ZSTK474 *Approval Status*: Phase I *Combination Therapy*: AZ628 + Selumetinib *Combination Therapy*: SAR260301 + Selumetinib *Combination Therapy*: BKM120 + Selumetinib	Colon Cancer, Colorectal Cancer, Malignant Glioma, Melanoma, Thyroid Cancer

Cetuximab Approved: Yes	*Drug Family*: EGFR mAb inhibitor *Alteration*: BRAF:V600E *Combination Therapy*: Dabrafenib + Cetuximab *Combination Therapy*: Encorafenib + Binimetinib + Cetuximab *Combination Therapy*: Vemurafenib + Cetuximab *Response Type*: sensitive *Approval Status*: Clinical Study *Evidence Type*: Actionable *Combination Therapy*: Cetuximab + FOLFOX *Response Type*: predicted – sensitive *Approval Status*: Phase II *Approval Status*: Preclinical *Combination Therapy*: Cetuximab + Irinotecan *Response Type*: resistant *Combination Therapy*: Cetuximab + Encorafenib *Approval Status*: Preclinical - Cell culture *Combination Therapy*: Cetuximab + Selumetinib *Combination Therapy*: Cetuximab + Dabrafenib + Trametinib *Combination Therapy*: LGX818 + Cetuximab + BYL719 *Combination Therapy*: Cetuximab + SCH772984 *Combination Therapy*: BI 882370 + Cetuximab *Combination Therapy*: BGB-283 + Cetuximab *Approval Status*: Preclinical - Cell line xenograft *Response Type*: predicted – resistant *Approval Status*: Guideline *Combination Therapy*: Cetuximab + Dabrafenib *Combination Therapy*: Cetuximab + Dabrafenib + SCH772984 *Combination Therapy*: Cetuximab + PLX4720 *Combination Therapy*: Regorafenib + Cetuximab *Combination Therapy*: Cetuximab + Selumetinib + Vemurafenib *Approval Status*: Preclinical - Pdx *Approval Status*: Phase Ib/II *Combination Therapy*: Vemurafenib + Cetuximab + Irinotecan *Clinical Status*: late trials *Pathway*: activation *Variant Effect*: gain-of-function	Colorectal Cancer
Arq-092 Approved: No	*Combination Therapy*: ARQ092 + Trametinib *Response Type*: sensitive *Approval Status*: Preclinical - Pdx *Evidence Type*: Actionable	Melanoma
Sorafenib Interaction type: inhibitor Approved: Yes	*Combination Therapy*: Sorafenib + Temsirolimus *Trial Name*: Nexavar *Novel Drug Target*: Established target *Drug Family*: Pan-TK inhibitor *Alteration*: BRAF:D594G,G469E *Alteration*: BRAF__. *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: conflicting *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: predicted – sensitive *Response Type*: sensitive *Approval Status*: Clinical Study *Combination Therapy*: Pimasertib + Sorafenib *Approval Status*: Preclinical - Cell culture *Response Type*: no benefit *Approval Status*: Phase II *Combination Therapy*: Cetuxmab + Sorafenib *Clinical Status*: preclinical *Pathway*: activation *Variant Effect*: gain-of-function (low activity)	Advanced Solid Tumor, Colon Cancer, Colorectal Cancer, Melanoma, Non-Small Cell Lung Carcinoma

Pilaralisib (Chembl3218575) Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Response Type*: decreased response *Approval Status*: Preclinical	Advanced Solid Tumor, Melanoma
Trastuzumab Approved: Yes	*Combination Therapy*: Fluorouracil + Leucovorin + Trastuzumab *Response Type*: no benefit *Approval Status*: Clinical Study *Evidence Type*: Actionable	Rectum Adenocarcinoma
Chembl525191 Interaction type: inhibitor Approved: No	*Response Type*: resistant *Approval Status*: Preclinical - Pdx *Evidence Type*: Actionable *Approval Status*: Preclinical - Cell line xenograft *Approval Status*: Preclinical - Pdx u0026 cell culture *Approval Status*: Preclinical - Cell culture *Response Type*: sensitive *Combination Therapy*: GDC0879 + GDC-0941 *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True	Colon Cancer, Melanoma, Non-Small Cell Lung Carcinoma, Pancreatic Cancer
Chembl458997 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Non-Small Cell Lung Carcinoma
Ganetespib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Combination Therapy*: Ganetespib + TAK-733	Melanoma, Non-Small Cell Lung Carcinoma, Skin Melanoma
Mln-2480 Interaction type: inhibitor Approved: No	*Mechanism Of Interaction*: RAF serine/threonine protein kinase inhibitor *Direct Interaction*: yes *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: sensitive *Approval Status*: Preclinical *Approval Status*: Phase I	Advanced Solid Tumor, Colorectal Cancer, Melanoma
Chembl523411 Interaction type: inhibitor Approved: No	*Trial Name*: GSK2118436 *Novel Drug Target*: Established target	
Plx-8394 Interaction type: inhibitor Approved: No	*Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Approval Status*: Preclinical - Cell culture *Approval Status*: Preclinical - Cell line xenograft *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Advanced Solid Tumor, Lung Adenocarcinoma, Melanoma
Dabrafenib Mesylate Interaction type: inhibitor Approved: Yes	*Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	

Sorafenib Tosylate Interaction type: inhibitor Approved: Yes	*Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	
Regorafenib Interaction type: inhibitor Approved: Yes	*Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True *Response Type*: resistant *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Pimasertib + Regorafenib *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Regorafenib + Cetuximab *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Breast Cancer, Colorectal Cancer
Ink-128 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: MLN0128 + PD-0325901 *Approval Status*: Preclinical - Cell line xenograft *Approval Status*: Preclinical - Cell culture	Colorectal Cancer
Mk-2206 Approved: No	*Combination Therapy*: MK2206 + Trametinib *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: MK2206 + Vemurafenib	Melanoma
Arq-736 Interaction type: inhibitor Approved: No	*Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes *Notes*: Targets wildtype BRAF and BRAF with V600E mutation	
Dasatinib Interaction type: inhibitor Approved: Yes	*Drug Family*: BCR-ABL inhibitor 2nd gen *Alteration*: BRAF:Y472C *Alteration*: BRAF:G466V *Clinical Status*: case report *Pathway*: activation *Variant Effect*: reduced kinase activity *Clinical Status*: preclinical *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: Dasatinib + Trametinib *Combination Therapy*: Dasatinib + SCH772984 *Approval Status*: Preclinical *Response Type*: resistant *Combination Therapy*: Dasatinib + Selumetinib	Lung Carcinoma, Melanoma, Non-Small Cell Lung Carcinoma, Thyroid Cancer
Nivolumab Approved: Yes		
Ro-4987655 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable	Melanoma

Alpelisib Approved: No	*Combination Therapy*: Panitumumab;Dabrafenib;BYL719 *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;PI3K inhibitor *Alteration*: BRAF:V600. *Combination Therapy*: LGX818 + Cetuximab + BYL719 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: resistant *Approval Status*: Phase Ib/II *Combination Therapy*: BYL719 + GSK2636771 *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: BYL719 + MEK162 *Response Type*: no benefit *Approval Status*: Preclinical *Combination Therapy*: BYL719 + LGX818 *Combination Therapy*: AZD6482 + LGX818 + BYL719 *Combination Therapy*: AZD6482 + Binimetinib + BYL719 *Combination Therapy*: AZD6482 + BYL719 *Combination Therapy*: BYL719 + GSK2636771 + LGX818 *Response Type*: decreased response *Combination Therapy*: BYL719 + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + BYL719 *Combination Therapy*: Alpelisib + PLX4720 *Combination Therapy*: ABT-263 + Alpelisib + Dabrafenib + Erlotinib	Colorectal Cancer, Melanoma
Panitumumab Approved: Yes	*Combination Therapy*: Panitumumab;Dabrafenib;BYL719 *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;PI3K inhibitor *Alteration*: BRAF:V600. *Combination Therapy*: Panitumumab;Dabrafenib;Trametinib *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E *Drug Family*: EGFR mAb inhibitor *Combination Therapy*: Vemurafenib;Panitumumab *Drug Family*: BRAF inhibitor;EGFR mAb inhibitor *Alteration*: MET:amp;BRAF:V600E *Clinical Status*: late trials *Pathway*: activation *Variant Effect*: gain-of-function *Combination Therapy*: Vemurafenib + Panitumumab *Combination Therapy*: Panitumumab + Dabrafenib *Response Type*: sensitive *Approval Status*: Phase I *Evidence Type*: Actionable *Response Type*: predicted – resistant *Approval Status*: Guideline *Approval Status*: Phase Ib/II *Approval Status*: Clinical Study *Response Type*: resistant *Approval Status*: Preclinical - Cell culture *Combination Therapy*: Irinotecan + Panitumumab *Response Type*: predicted – sensitive *Combination Therapy*: Panitumumab + Trametinib + Dabrafenib	Colon Cancer, Colorectal Cancer

Encorafenib Interaction type: inhibitor Approved: No	*Combination Therapy*: LGX818 + Cetuximab + BYL719 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: resistant *Combination Therapy*: AZD6482 + LGX818 *Response Type*: no benefit *Approval Status*: Preclinical *Combination Therapy*: GSK2636771 + LGX818 *Approval Status*: Phase Ib/II *Combination Therapy*: LGX818 + unspecified IGF-1R antibody *Combination Therapy*: BYL719 + LGX818 *Combination Therapy*: AZD6482 + LGX818 + BYL719 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + NVP-AEW541 *Combination Therapy*: GSK2636771 + LGX818 + unspecified IGF-1R antibody *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: AZD6482 + LGX818 + NVP-AEW541 *Combination Therapy*: BYL719 + GSK2636771 + LGX818 *Combination Therapy*: GDC-0941 + LGX818 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + BYL719 *Combination Therapy*: CGM097 + LGX818 *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes *Combination Therapy*: Encorafenib + Binimetinib + Cetuximab *Combination Therapy*: Cetuximab + Encorafenib *Combination Therapy*: Encorafenib + Ribociclib *Approval Status*: Phase I *Combination Therapy*: Binimetinib + Encorafenib *Combination Therapy*: Encorafenib + BKM120	Advanced Solid Tumor, Colorectal Cancer, Melanoma
Palbociclib Approved: Yes	*Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: Palbociclib + Trametinib *Response Type*: decreased response *Response Type*: no benefit *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: PD-0325901 + Palbociclib *Approval Status*: Preclinical - Pdx	Colorectal Cancer, Melanoma
Chembl373011 Interaction type: inhibitor Approved: No	*Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False	
Fluorouracil Approved: Yes	*Combination Therapy*: Fluorouracil + Leucovorin + Trastuzumab *Response Type*: no benefit *Approval Status*: Clinical Study *Evidence Type*: Actionable *Combination Therapy*: DT01 + Fluorouracil + Oxaliplatin *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft	Colorectal Cancer, Rectum Adenocarcinoma

Azd-6482 Approved: No	*Combination Therapy*: AZD6482 + NVP-AEW541 *Response Type*: no benefit *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: AZD6482 + LGX818 *Combination Therapy*: AZD6482 + Binimetinib *Response Type*: sensitive *Combination Therapy*: AZD6482 + LGX818 + BYL719 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + BYL719 *Approval Status*: Preclinical - Cell culture *Combination Therapy*: AZD6482 + LGX818 + NVP-AEW541 *Combination Therapy*: AZD6482 + BYL719 *Combination Therapy*: AZD6482 + Binimetinib + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + BYL719	Melanoma
Sar-260301 Approved: No	*Combination Therapy*: SAR260301 + Selumetinib *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Combination Therapy*: SAR260301 + Vemurafenib	Melanoma
Erlotinib Approved: Yes	*Combination Therapy*: Erlotinib + PLX4720 *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Combination Therapy*: Vemurafenib + Erlotinib *Combination Therapy*: ABT-263 + Alpelisib + Dabrafenib + Erlotinib *Approval Status*: Preclinical - Cell culture	Colorectal Cancer, Melanoma
Saracatinib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma
Gefitinib Approved: Yes	*Combination Therapy*: Vemurafenib + Gefitinib *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Gefitinib + PLX4720 *Response Type*: resistant *Approval Status*: Preclinical - Cell culture	Colorectal Cancer, Melanoma
Chembl1231206 Approved: No	*Combination Therapy*: PF3644022 + PF-477736 *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Patient cell culture *Evidence Type*: Actionable *Approval Status*: Preclinical - Cell culture *Approval Status*: Preclinical - Cell line xenograft	Advanced Solid Tumor, Colon Cancer, Lung Adenocarcinoma
Plx-3397 Approved: No	*Combination Therapy*: PLX3397 + Vemurafenib *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma
Imatinib Approved: Yes	*Response Type*: sensitive *Approval Status*: Guideline *Evidence Type*: Actionable *Combination Therapy*: Imatinib + PLX4720 *Approval Status*: Preclinical - Cell line xenograft	Melanoma

Neratinib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Colorectal Cancer
E-6201 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: decreased response *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: E6201 + LY294002	Melanoma
Capmatinib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Pdx *Evidence Type*: Actionable *Combination Therapy*: INC280 + Trametinib	Collecting Duct Carcinoma
Refametinib Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable *Approval Status*: Preclinical	Colorectal Cancer, Melanoma
Chir-265 Interaction type: inhibitor Approved: No	*Trial Name*: CHIR-265 *Novel Drug Target*: Established target *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: resistant *Response Type*: predicted – sensitive *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Advanced Solid Tumor, Melanoma
Ribociclib Approved: Yes	*Combination Therapy*: Encorafenib + Ribociclib *Response Type*: sensitive *Approval Status*: Phase Ib/II *Evidence Type*: Actionable	Melanoma
Bi-2536 Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: BI2536 + PLX4720 *Approval Status*: Preclinical - Cell line xenograft	Glioblastoma Multiforme
Pd-0325901 Approved: No	*Response Type*: resistant *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Response Type*: decreased response *Approval Status*: Preclinical - Cell culture *Response Type*: conflicting *Combination Therapy*: PD-0325901 + Palbociclib *Combination Therapy*: MLN0128 + PD-0325901	Colon Cancer, Colorectal Cancer, Glioblastoma Multiforme, Melanoma
Navitoclax Approved: No	*Combination Therapy*: Trametinib + Navitoclax *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: PLX4720 + Navitoclax *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Navitoclax + Vemurafenib *Combination Therapy*: ABT-263 + Alpelisib + Dabrafenib + Erlotinib *Approval Status*: Preclinical - Cell culture *Combination Therapy*: ABT-263 + CGM097 + Dabrafenib + PF-04217903	Colon Cancer, Colorectal Cancer, Melanoma, Non-Small Cell Lung Carcinoma

Chembl526479 Approved: No		
Atezolizumab Approved: Yes	*Combination Therapy*: Atezolizumab + Vemurafenib + Cobimetinib *Response Type*: sensitive *Approval Status*: Phase Ib/II *Evidence Type*: Actionable	Melanoma
Everolimus Approved: Yes	*Combination Therapy*: Everolimus + Selumetinib *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: resistant *Approval Status*: Clinical Study *Combination Therapy*: Dabrafenib + Everolimus + Trametinib *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Everolimus + PLX4720 *Combination Therapy*: Everolimus + Pimasertib	Colorectal Cancer, Malignant Glioma, Melanoma, Thyroid Carcinoma
Dactolisib Approved: No	*Combination Therapy*: BEZ235 + Vemurafenib *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Selumetinib + BEZ235 *Approval Status*: Preclinical - Cell line xenograft	Melanoma
Pimasertib Approved: No	*Combination Therapy*: Pimasertib + Sorafenib *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Combination Therapy*: Pimasertib + Regorafenib *Combination Therapy*: Everolimus + Pimasertib	Colorectal Cancer
Gsk-2636771 Approved: No	*Combination Therapy*: GSK2636771 + unspecified PD-1 antibody *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: GSK2636771 + Binimetinib *Response Type*: no benefit *Combination Therapy*: GSK2636771 + LGX818 *Combination Therapy*: GSK2636771 + NVP-AEW541 *Combination Therapy*: BYL719 + GSK2636771 *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: GSK2636771 + LGX818 + unspecified IGF-1R antibody *Combination Therapy*: BYL719 + GSK2636771 + LGX818 *Combination Therapy*: GSK2636771 + unspecified IGF-1R antibody *Combination Therapy*: GSK2636771 + Pembrolizumab	Melanoma
Ly-3009120 Interaction type: inhibitor Approved: No	*Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Response Type*: decreased response *Approval Status*: Preclinical - Cell culture *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Hematologic Cancer, Melanoma, Non-Small Cell Lung Carcinoma, Ovarian Cancer, Pancreatic Cancer

Cediranib Approved: No	*Combination Therapy*: Cediranib + Selumetinib + PLX4720 *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Cediranib + PLX4720 *Approval Status*: Preclinical - Cell line xenograft	Melanoma
Obatoclax Approved: No	*Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable	Advanced Solid Tumor
Binimetinib Approved: No	*Combination Therapy*: Encorafenib + Binimetinib + Cetuximab *Combination Therapy*: Binimetinib + BKM120 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Approval Status*: Phase II *Combination Therapy*: Binimetinib + Encorafenib *Approval Status*: Phase Ib/II *Combination Therapy*: GSK2636771 + Binimetinib *Response Type*: no benefit *Approval Status*: Preclinical *Combination Therapy*: AZD6482 + Binimetinib *Response Type*: predicted – sensitive *Approval Status*: Phase I *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + BYL719 *Combination Therapy*: GDC-0941 + Binimetinib *Combination Therapy*: AZD6482 + Binimetinib + NVP-AEW541 *Combination Therapy*: AZD6482 + Binimetinib + LGX818 + BYL719 *Combination Therapy*: BYL719 + MEK162	Advanced Solid Tumor, Colorectal Cancer, Melanoma
Chembl217354 Approved: No	*Combination Therapy*: Trametinib + TW-37 *Response Type*: sensitive *Approval Status*: Preclinical *Evidence Type*: Actionable *Combination Therapy*: Vemurafenib + TW-37	Melanoma, Non-Small Cell Lung Carcinoma
Bgb-283 Interaction type: inhibitor Approved: No	*Details Of The Assay For Interaction*: Inhibition of wild type BRAF kinase domain (aa416-766) *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: False *Response Type*: resistant *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: sensitive *Combination Therapy*: BGB-283 + Cetuximab *Approval Status*: Preclinical - Cell line xenograft *Approval Status*: Preclinical - Pdx u0026 cell culture *Approval Status*: Phase I *Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Advanced Solid Tumor, Colorectal Cancer, Melanoma, Thyroid Cancer
Paclitaxel Approved: Yes	*Combination Therapy*: Selumetinib + Paclitaxel	

Tak-733 Approved: No	*Response Type*: sensitive *Approval Status*: Phase I *Evidence Type*: Actionable *Combination Therapy*: Ganetespib + TAK-733 *Approval Status*: Preclinical - Cell line xenograft *Response Type*: predicted – sensitive *Approval Status*: Preclinical - Pdx u0026 cell culture	Colorectal Cancer, Melanoma
Crizotinib Approved: Yes	*Combination Therapy*: Crizotinib;Vemurafenib *Drug Family*: ALK inhibitor;BRAF inhibitor *Alteration*: MET:amp;BRAF:V600E	
Venetoclax Approved: Yes	*Combination Therapy*: Venetoclax + VX-11e *Response Type*: no benefit *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable	Colorectal Cancer
Idelalisib Approved: Yes	*Response Type*: no benefit *Approval Status*: Preclinical *Evidence Type*: Actionable	Melanoma

Dabrafenib Interaction type: inhibitor Approved: Yes	*Combination Therapy*: Dabrafenib;Trametinib *Drug Family*: BRAF inhibitor;MEK inhibitor *Alteration*: BRAF:V600E *Combination Therapy*: Panitumumab;Dabrafenib;BYL719 *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;PI3K inhibitor *Alteration*: BRAF:V600. *Combination Therapy*: Panitumumab;Dabrafenib;Trametinib *Drug Family*: EGFR mAb inhibitor;BRAF inhibitor;MEK inhibitor *Drug Family*: BRAF inhibitor *Alteration*: BRAF:V600R *Alteration*: BRAF:V600E,V600K *Specific Action Of The Ligand*: Inhibition *Endogenous Drug*: False *Direct Interaction*: True *Combination Therapy*: Dabrafenib + Cetuximab *Combination Therapy*: Panitumumab + Dabrafenib *Combination Therapy*: Dabrafenib + Trametinib *Notes*: Targets mutant BRAF kinases *Combination Therapy*: Trametinib + Dabrafenib *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Response Type*: decreased response *Combination Therapy*: Dabrafenib + Everolimus + Trametinib *Approval Status*: Clinical Study *Response Type*: resistant *Approval Status*: Preclinical *Combination Therapy*: Cetuximab + Dabrafenib + Trametinib *Combination Therapy*: Dabrafenib + GSK2126458 *Approval Status*: FDA approved *Approval Status*: Guideline *Approval Status*: Phase II *Combination Therapy*: Dabrafenib + SCH772984 *Combination Therapy*: Cetuximab + Dabrafenib *Combination Therapy*: Cetuximab + Dabrafenib + SCH772984 *Approval Status*: Phase Ib/II *Response Type*: no benefit *Response Type*: conflicting *Approval Status*: Phase III *Approval Status*: Phase I *Combination Therapy*: Panitumumab + Trametinib + Dabrafenib *Response Type*: predicted – sensitive *Combination Therapy*: ABT-263 + Alpelisib + Dabrafenib + Erlotinib *Combination Therapy*: ABT-263 + CGM097 + Dabrafenib + PF-04217903 *Combination Therapy*: AMG 232 + Trametinib + Dabrafenib *Response Type*: predicted – resistant *Clinical Status*: FDA-approved *Pathway*: activation *Variant Effect*: gain-of-function *Clinical Status*: early trials *Clinical Status*: case report	Advanced Solid Tumor, Colorectal Cancer, Melanoma, Neuroendocrine Tumor, Non-Small Cell Lung Carcinoma, Ovarian Cancer, Pancreatic Cancer, Pilocytic Astrocytoma, Thyroid Cancer, Thyroid Carcinoma
Rg-7256 Interaction type: inhibitor Approved: No	*Mechanism Of Interaction*: Serine/threonine-protein kinase B-raf inhibitor *Direct Interaction*: yes	Melanoma

Pf-04217903 Approved: No	*Combination Therapy*: ABT-263 + CGM097 + Dabrafenib + PF-04217903 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable	Colorectal Cancer
Pa-799 Approved: No	*Response Type*: decreased response *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable	Breast Cancer
Leucovorin Approved: Yes	*Combination Therapy*: Fluorouracil + Leucovorin + Trastuzumab *Response Type*: no benefit *Approval Status*: Clinical Study *Evidence Type*: Actionable	Rectum Adenocarcinoma
Oxaliplatin Approved: Yes	*Combination Therapy*: DT01 + Fluorouracil + Oxaliplatin *Response Type*: sensitive *Approval Status*: Preclinical - Cell line xenograft *Evidence Type*: Actionable	Colorectal Cancer
Buparlisib Approved: No	*Combination Therapy*: Binimetinib + BKM120 *Response Type*: sensitive *Approval Status*: Preclinical - Cell culture *Evidence Type*: Actionable *Approval Status*: Preclinical - Cell line xenograft *Combination Therapy*: Encorafenib + BKM120 *Combination Therapy*: BKM120 + Selumetinib *Combination Therapy*: BKM120 + Vemurafenib *Combination Therapy*: BKM120 + Trametinib	Melanoma

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