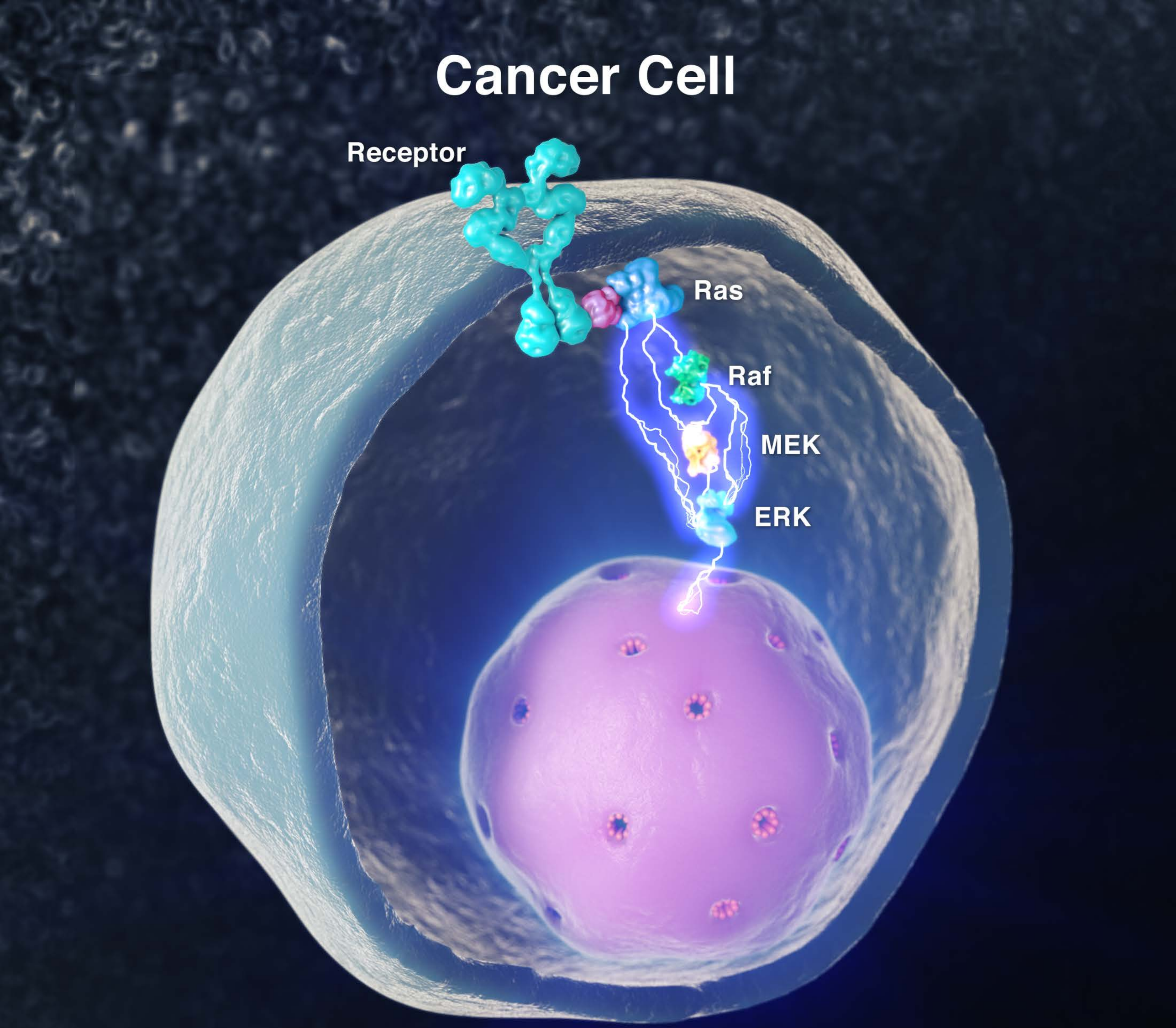
Cancer Cell



A series of proteins called the MAPK cell signaling pathway help control cell growth and survival. When some BRAF proteins are mutated in advanced melanoma, abnormal growth signals are continuously sent into the cell causing tumors to grow.

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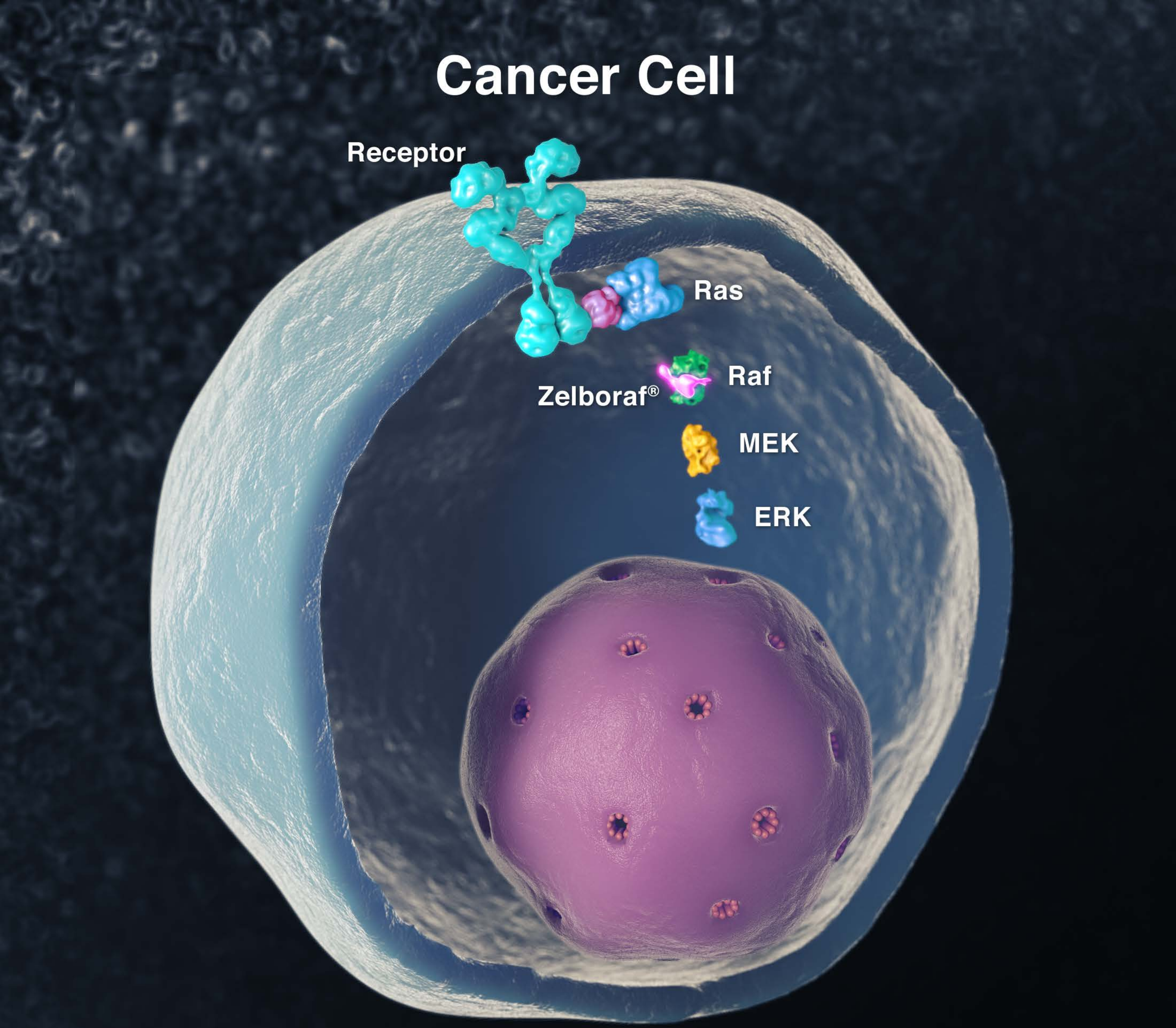

Zelboraf® (vemurafenib) is designed to work inside melanoma cells to inhibit some mutated forms of BRAF.

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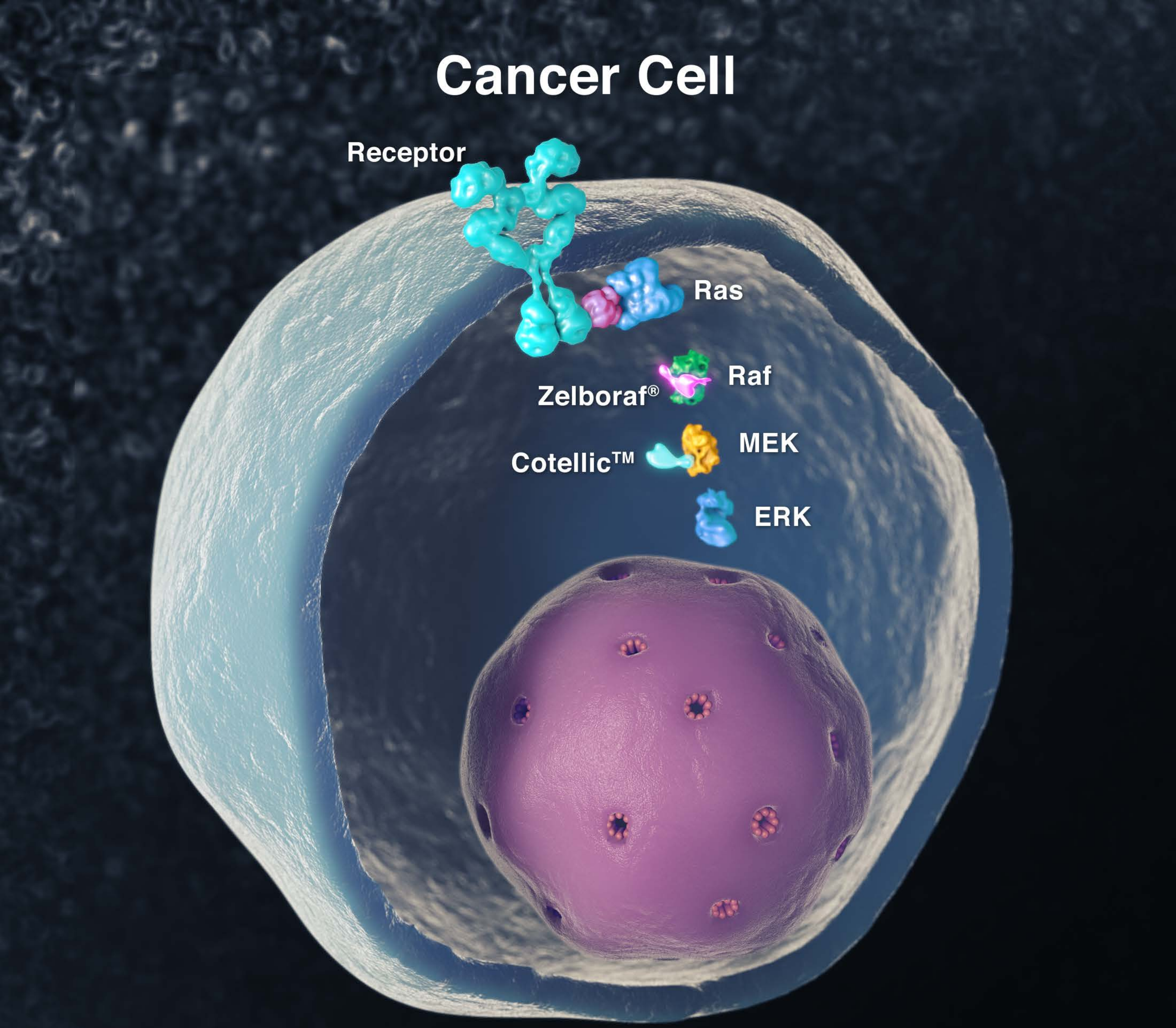

Cotellic™ (cobimetinib) is an inhibitor of some forms of MEK, a protein in the same cell signaling pathway and also found in melanoma cells. When used in combination, Cotellic and Zelboraf are thought to reduce cancer cell growth compared to Zelboraf alone.

Cotellic Indication Statement

Cotellic is a prescription medicine that is used with Zelboraf (vemurafenib), to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and that has a certain type of abnormal "BRAF" gene.

A patient's healthcare provider will perform a test for the BRAF gene to make sure that Cotellic is right for the patient. Cotellic is not used to treat melanoma with a normal BRAF gene.

It is not known if Cotellic is safe and effective in children under 18 years of age.

Cotellic Important Safety Information

Before taking Cotellic, patients should tell their doctor if they:

- have any previous or current skin problems other than melanoma
- have any medical conditions and/or are on any medications that increase your risk of bleeding
- have any heart problems
- have any eye problems
- have any liver problems
- have any muscle problems
- have any other medical conditions
- are pregnant or plan to become pregnant. Cotellic can harm an unborn baby.
    - Patients who take Cotellic should use effective methods of birth control during treatment, for at least two weeks after stopping Cotellic, and for at least two months after stopping Zelboraf.
    - Patients should talk to their healthcare provider about birth control methods that may be right for them.
    - Patients should tell their healthcare provider right away if they become pregnant or think they are pregnant during treatment with Cotellic.
- are breastfeeding or plan to breastfeed. It is not known if Cotellic passes into breast milk, so patients should not breastfeed during treatment with Cotellic and for two weeks after the final dose. Patients should talk to their healthcare provider about the best way to feed their baby during this time.

Patients should tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements because some types of medicines will make Cotellic more harmful or less effective. Patients should know the medicines they take and keep a list of them to show their healthcare provider and pharmacist when they get a new medicine.

Patients should avoid sunlight while taking Cotellic. Cotellic can make patients' skin sensitive to sunlight and cause them to burn more easily and get severe sunburns. To help protect against sunburn:

- When patients go outside they should wear clothes that protect their skin, including their head, face, hands, arms and legs.
- Patients should use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

Cotellic may cause serious side effects, including:

- **Risk of skin cancers.** Cotellic may cause skin cancers (cutaneous squamous cell

carcinoma, keratoacanthoma or basal cell carcinoma).

Patients must check their skin and tell their doctor right away about any skin changes, including:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

A patient's healthcare provider should check their skin before they start taking Cotellic and every two months while taking Cotellic. A patient's healthcare provider may continue to check their skin for six months after they stop taking Cotellic.

- **Increased risk of bleeding.** Cotellic may cause bleeding, including blood in the urine, rectal bleeding, unusual or excessive vaginal bleeding, bleeding of the gums and bleeding within the brain (cerebral hemorrhage).
  A patient should tell their healthcare provider right away if they experience any of these symptoms:
  - red or black stools that look like tar
  - blood in the urine
  - headache, dizziness or feeling weak
  - abdominal pain
  - unusual vaginal bleeding

- **Heart problems that can lead to inadequate pumping of the blood by the heart.** A patient's healthcare provider should perform tests before the patient starts taking Cotellic and during a patient's treatment with Cotellic to check the ability of the heart to pump blood. Signs and symptoms of a decrease in the amount of blood pumped include:
  - persistent coughing or wheezing
  - shortness of breath
  - swelling of their ankles and feet
  - tiredness
  - increased heart rate

- **Rash.** Patients should tell their healthcare provider right away if they experience any of these symptoms:
  - a rash that covers a large area of their body, blisters or peeling skin

- **Eye problems.** Patients should tell their healthcare provider right away if they experience any of these symptoms during treatment with Cotellic:
  - blurred vision
  - distorted vision
  - partly missing vision
  - halos
  - any other vision changes

  Some of these eye problems may be a result of something called "serous retinopathy" (a build-up of fluid under the retina of the eye). A patient's healthcare provider should check their eyes if they notice any of the symptoms above.

- **Abnormal liver test or liver injury.** A patient's healthcare provider should perform blood tests before the start taking Cotellic, and during treatment. A patient should tell their healthcare provider right away if you experience any of these symptoms:
    - yellowing of their skin or the white of their eyes
    - dark or brown (tea color) urine
    - nausea or vomiting
    - feeling tired or weak
    - loss of appetite

- **Increased levels of an enzyme in the blood.** Creatine phosphokinase (CPK) is an enzyme that is primarily found in the muscle, heart and brain. Treatment with Cotellic may increase the level of this enzyme in your blood and be a sign of muscle damage. A patient's healthcare provider should perform a blood test before and during treatment. Increased blood levels of CPK can also be an indication of a serious condition caused by injury to the muscles (rhabdomyolysis). A patient should tell their healthcare provider right away if they experience any of these symptoms:
    - muscle aches
    - muscle spasms and weakness
    - dark, reddish urine

- **Photosensitivity.** A patient's skin may become more sensitive to sunlight while taking Cotellic. A patient should tell their healthcare provider if they notice any of the following symptoms:
    - red, painful, itchy skin that is hot to touch
    - sun rash
    - skin irritation bumps or tiny papules
    - thicken, dry, wrinkled skin

The most common side effects of Cotellic include:

- diarrhea
- sunburn or sun sensitivity
- nausea
- vomiting
- fever

A patient's healthcare provider will take blood tests while they are taking Cotellic. The most common changes to blood tests include:

- increased blood levels of liver enzymes (GGT, ALT or AST)
- increased blood level of enzyme from muscle (creatine phosphokinase)
- decreased blood level of phosphate, sodium or potassium
- increased blood level of liver or bone enzyme (alkaline phosphatase)
- decreased blood level of a type of white blood cell (lymphocyte)

Patients should tell their healthcare provider if they have any side effect that bothers them or that does not go away.

These are not all the possible side effects of Cotellic. For more information about side effects, patients should ask their healthcare provider or pharmacist. Patients should call their doctor for medical advice about side effects.

Patients should talk to their doctor for medical advice about side effects. Report side effects to FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see full Cotellic Prescribing Information and Patient Information for additional important safety information.