

A summary of safety information of drugs used in Cosmic 21 study (Exelixis)

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ATEZOLIZUMAB

Possible side effects with Atezolizumab used alone:

Very common: (may affect more than 1 in 10 people)

• Fever • nausea • vomiting • feeling very tired with no energy (fatigue) • lack of energy • itching of the skin • diarrhoea • joint pain • rash • loss of appetite • shortness of breath • urinary tract infection • back pain • cough • pain in the muscles and bones

Common: (may affect up to 1 in 10 people)

• Inflammation of the lungs (pneumonitis) • low oxygen levels, which may cause shortness of breath as a consequence of inflamed lungs (hypoxia) • stomach pain • inflammation of the liver • elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver • difficulty swallowing • blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia) • low blood pressure (hypotension) • underactive thyroid gland (hypothyroidism) • allergic reaction (infusion-related reaction, hypersensitivity or anaphylaxis) • flu-like illness • chills • inflammation of the intestines • low platelet count, which may make you more likely to bruise or bleed • blocked nose (nasal congestion) • high blood sugar • common cold • mouth and throat pain

Uncommon: (may affect up to 1 in 100 people)

• Inflammation of the pancreas • numbness or paralysis, which may be signs of Guillain-Barre syndrome • inflammation of the membrane around the spinal cord and brain • low levels of adrenal hormones • overactive thyroid gland (hyperthyroidism) • type 1 diabetes • inflammation of muscles (myositis) • red, dry, scaly patches of thickened skin (psoriasis)

Rare: (may affect up to 1 in 1,000 people)

• Inflammation of the heart muscle • myasthenia gravis, an illness that can cause muscle weakness • inflammation of the pituitary gland situated at the base of the brain • inflammation of the kidneys • inflammation of the eye (uveitis)

Atezolizumab used in combination with anticancer medicines

The following side effects have been reported in clinical trials when Atezolizumab is given in combination with anticancer medicines:

Very common: may affect more than 1 in 10 people

• low number of red blood cells, which can cause tiredness and shortness of breath • low white blood cell count with and without fever, which can increase the risk of infection (neutropenia,

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leukopenia) • low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia) • constipation • nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy) • underactive thyroid gland (hypothyroidism) • loss of appetite • shortness of breath • diarrhoea • nausea • itching of the skin • rash • joint pain • feeling very tired (fatigue) • fever • headache • cough • pain in the muscles and bones • vomiting • back pain • lack of energy • dizziness • infection of the lung • blood test showing low levels of magnesium (hypomagnesaemia) • hair loss • high blood pressure (hypertension)

Common: may affect up to 1 in 10 people

- Blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia) • inflammation of the mouth or lips • hoarse voice (dysphonia) • low levels of magnesium, which can cause weakness and muscle cramping, numbness and pain in the arms and legs • protein in urine (proteinuria) • fainting • elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver • changes to sense of taste (dysgeusia) • decreased number of lymphocyte (a type of white blood cells), which is associated with an increased risk of infection • abnormal kidney test (possible kidney damage) • low lymphocyte count, which can increase the risk of infection (lymphopenia) • overactive thyroid gland (hyperthyroidism)

Uncommon: may affect up to 1 in 100 people

- Red, dry, scaly patches of thickened skin (psoriasis)

CABOZANTINIB

Possible side effects

- Symptoms including pain in the abdomen, nausea (feeling sick), vomiting, constipation, or fever. These may be signs of a gastrointestinal perforation, a hole that develops in your stomach or intestine that could be life-threatening.
- Severe or uncontrollable bleeding with symptoms such as: vomiting blood, black stools, bloody urine, headache, coughing up blood.
- Swelling, pain in your hands and feet, or shortness of breath.
- A wound that does not heal.
- Fits, headaches, confusion, or finding it difficult to concentrate. These may be signs of a condition called posterior reversible encephalopathy syndrome (PRES). PRES is rare (it affects less than 1 in 1000 people).
- Feeling drowsy, confused or loss of consciousness. This may be due to liver problems.
- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis).

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion and abdominal pain,
- Blisters, pain of the hands or soles of the feet, rash or redness of the skin
- Decreased appetite, weight loss, altered sense of taste
- Fatigue, weakness, headache, dizziness
- Hypertension (increase in blood pressure)
- Anaemia (low levels of red blood cells)
- Low level of platelets
- Redness, swelling or pain in the mouth or throat, Difficulty in speaking, hoarseness, cough
- Changes

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in blood tests used to monitor general health and function of your organs (including the liver, and kidney), low levels of electrolytes (like magnesium, or potassium) • Shortness of breath • Reduced thyroid activity; symptoms can include: tiredness, weight gain, constipation, feeling cold and dry skin • Swelling in your legs and arms • Pain in the arms, hands, legs or feet • Low level of albumin in blood

Common side effects (may affect up to 1 in 10 people)

• Abscess (collection of pus, with swelling and inflammation) • Dehydration • Difficulty in swallowing • Ringing in ears • Blood clots in the blood vessels and lungs • Low level of white blood cells • Increased or decreased blood sugar level • Decrease in levels of; calcium, sodium and phosphate in the blood • Increase in level of potassium in the blood • Increase in the level of bilirubin in the blood (which may result in jaundice/yellow skin or eyes) • Increase in amylase levels in the blood • Increase in lipase levels in the blood • Increase in cholesterol or triglyceride levels in the blood • Numbness, tingling, burning sensation or pain in the limbs • A painful tear or abnormal connection of the tissues in your body • Gastro-oesophageal reflux disease (bringing up stomach acid) • Haemorrhoids (piles) • Dry mouth and pain in the mouth • Feeling drowsy, confused or loss of consciousness due to liver problems • Dry skin, severe itching of skin, acne • Thickening of the skin outer layer • Alopecia (hair loss and thinning), hair colour change • Pain in joints, muscle spasms • Protein in urine (seen in tests) • A burning or stinging sensation of the tongue

Uncommon side effects (may affect 1 in 100 people)

• Fits • Inflammation of the pancreas • Decrease in bile flow from the liver • Bone damage in the jaw • Wound complications

Not known/ Rare (proportion of people affected not known)

• Stroke • Posterior reversible encephalopathy syndrome (PRES) • Heart attack • An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)

References:

1) Summary of product characteristics for Atezolizumab. European Medicines Agency.

https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf

2) Summary of product characteristics for cabozantinib. European Medicines Agency.

https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf.