

Gemcitabine, cisplatin and durvalumab (GEM/CIS/DURVA) for biliary tract cancers

If your doctor recommended the combination of gemcitabine and cisplatin plus durvalumab to treat your cancer, here is some important information about these medications and some aspects related to them.

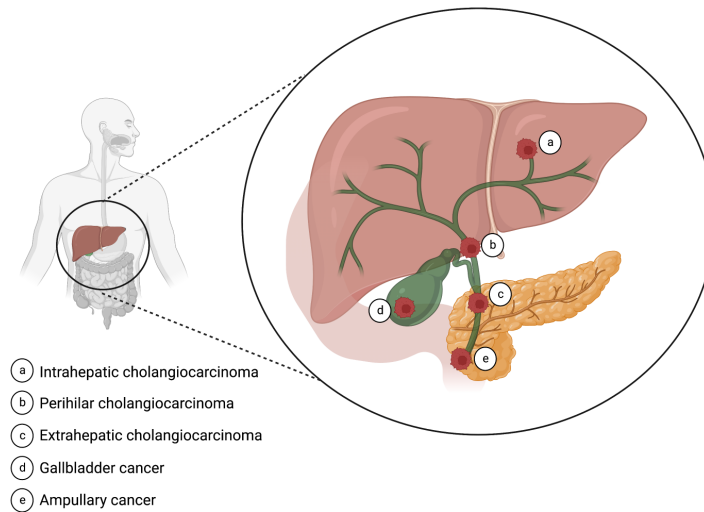
Biliary tract cancer

Biliary tract cancers develop from cells (called cholangiocytes) that normally make up the lining of the biliary system (depicted in green in the picture below). The biliary ducts are small tubes that connect the liver and gallbladder to the small bowel and normally carry the bile, which is a fluid that helps to digest food.

Biliary tract cancers include cholangiocarcinoma, gallbladder cancer and ampullary cancer:

- **Cholangiocarcinoma** - arises from the bile ducts. This cancer is further classified into three different types, depending on which part of the bile duct the cancer develops:
 - *intrahepatic cholangiocarcinoma* - the cancer develops in the ducts inside the liver
 - *perihilar cholangiocarcinoma* - it develops in the ducts just outside the liver
 - *distal/extrahepatic cholangiocarcinoma* - it develops in the ducts further away from the liver
- **Gallbladder cancer** - arises from the cells of the gallbladder
- **Ampullary cancer** - arises from the join between the bile ducts and the small bowel, called ampulla of Vater

You have been given this leaflet because you have been diagnosed with a biliary tract cancer. Your oncologist can discuss with you which biliary tract cancer you have and how extended it is.



What is GEM/CIS/DURVA?

Gemcitabine and cisplatin are two chemotherapy drugs which kill tumour cells by interfering with the process of cell replication. Durvalumab is an immunotherapy drug and is also called checkpoint inhibitor. It stimulates the body's immune system to recognise and fight cancer cells. We will call the combination of gemcitabine and cisplatin plus durvalumab with the shorter name GEM/CIS/DURVA.

How is GEM/CIS/DURVA administered?

You will receive GEM/CIS/DURVA in hospital, in the chemotherapy unit. All three drugs are injected intravenously (into a vein) through a *cannula*, a short thin tube, which will be put into a vein in your arm or hand by a nurse. The cannula will be removed after you receive GEM/CIS/DURVA. Cisplatin may cause some pain or be harmful along the vein, and may be toxic for your kidney, therefore you will receive plenty of fluids into your vein before and after the cisplatin infusion to prevent this.

Your doctor will decide the exact dosage of gemcitabine and cisplatin you will receive based on your height, weight, age, general health, and underlying conditions. Durvalumab will be administered at a standard flat dose.

Schedule of GEM/CIS/DURVA treatment

You will receive GEM/CIS/DURVA in cycles of treatment. The standard schedule of GEM/CIS/DURVA treatment follows a three-week cycle, involving one day of treatment a week, for two weeks, followed by one week of rest.

Before each session of treatment, you will have a blood test and your oncological team will check whether you are fit enough for the infusion. It is important that you report any symptom(s) and problem(s) since your last session so that the dose/schedule can be adjusted and personalised specifically for you.

Phase A: in this phase chemotherapy and durvalumab will be administered together for a maximum of 8 cycles, every three weeks.

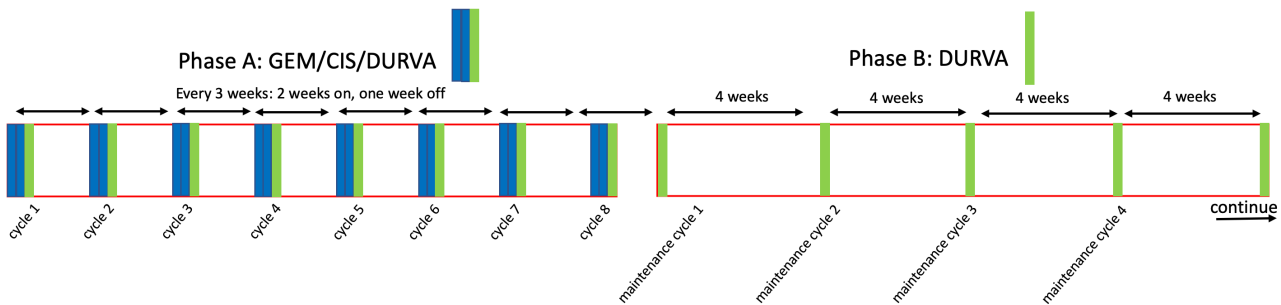
On DAY 1 of the first week of each cycle, you will come to hospital to see the oncology team to be assessed and have a blood test. You will come back 1 or 2 days later to receive chemotherapy and immunotherapy. On this occasion you will not meet the doctor unless you have developed some issues. The chemotherapy session will last for 3 to 4 hours. The immunotherapy session will last for 1 hour.

On DAY 8 of the second week, you will need to repeat the bloods, but the team can assess you by phone before you come to hospital for your chemotherapy. You will not receive durvalumab. The doctor may ask you to have the bloods taken at your GP practice the day before your treatment appointment.

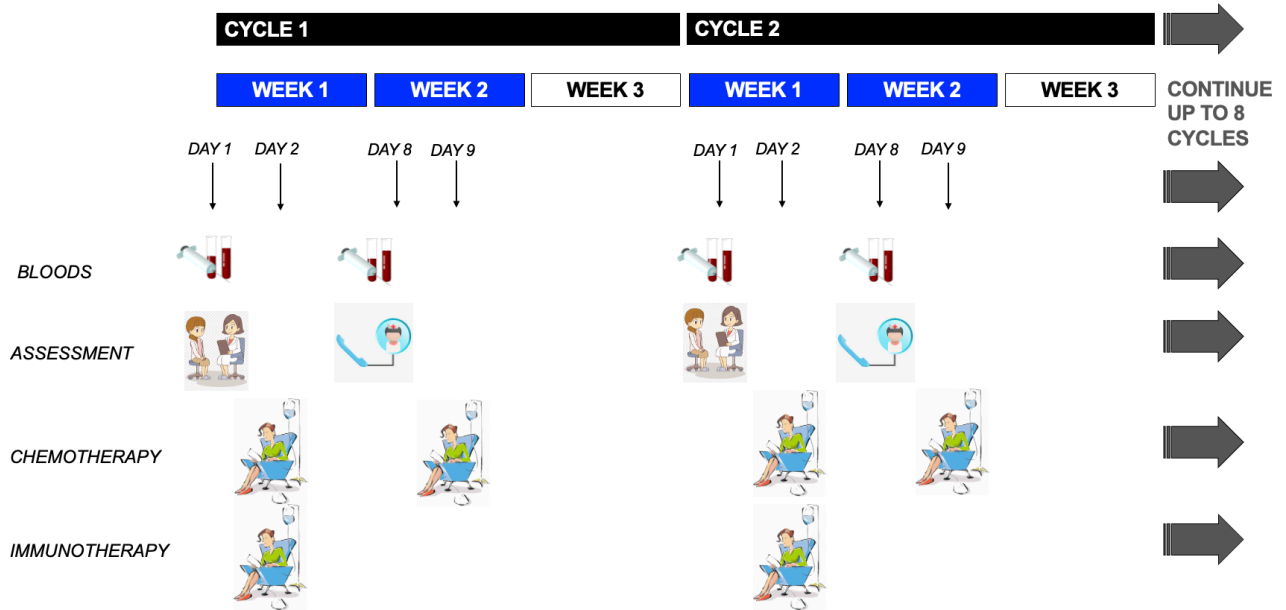
Phase B: it is also called maintenance phase.

During MAINTENANCE treatment, only durvalumab will be administered at a flat dose every 4 weeks.

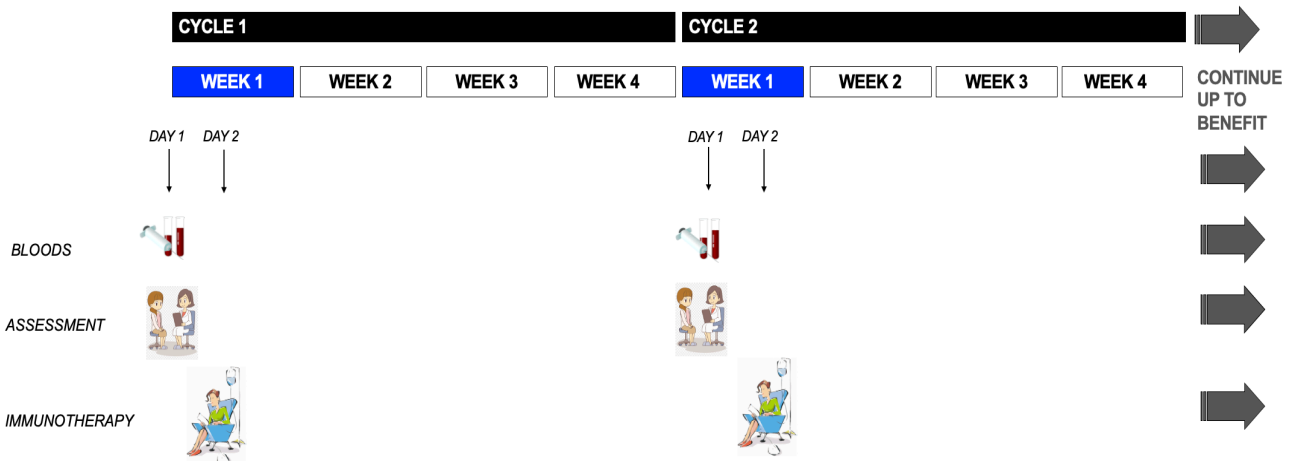
You will not need to stay in hospital overnight.



Phase A: GEM/CIS/DURVA cycle: 2 weeks on, 1 week off



Phase B: DURVA maintenance: every 4 weeks



Duration of GEM/CIS/DURVA treatment

The doctor will discuss the duration of your treatment with you. Each GEM/CIS/DURVA cycle will last for 3 weeks. If you are tolerating the treatment well, you will receive chemoimmunotherapy for at least 3 months before you will repeat scan to understand if the treatment is working. If the first 3 months scan shows your cancer is stable or shrinking, you may continue the treatment for another 3 months. After the first 6 months of combined treatment (up to a maximum of 8 cycles of chemotherapy), your doctor will discuss with you whether you should continue with maintenance treatment with durvalumab alone. It will be administered at a flat dose every 4 weeks until well tolerated. You will repeat scan every 3 months to assess tumour response to maintenance treatment.

What are the side effects of the GEM/CIS/DURVA treatment?

There are known side effects with this treatment, but you may not experience any of them. This does not mean that the treatment is not working. There is no relationship between the presence or severity of side effects and the efficacy of the chemoimmunotherapy.

You may get some of the side effects, but you are unlikely to get them all. Importantly, side effects are often predictable in terms of their onset, duration, and severity; they are almost always reversible and, except for those related to cisplatin, should completely go away after treatment. However, their frequency and severity may vary from person to person.

As with many other chemotherapy drugs, gemcitabine and cisplatin kill cancer cells because of their ability to stop cell division and proliferation. Unfortunately, chemotherapy drugs are not able to distinguish between cancerous cells and normal cells. So, chemotherapy will also kill normal cells that are rapidly dividing, like blood cells, cells in the mouth, stomach, bowel and elsewhere, which is what causes some of the different side effects. Once treatment ends, those normal cells will grow back and be healthy again.

Durvalumab is an immunotherapy drug that stimulates the body's immune system to recognise and fight cancer cells. Because it affects the whole immune system, it may cause inflammation in any part of the body, leading to potentially side effects that should be reported as soon as possible.

Fortunately, there are many medications available that can be taken during treatment to control and minimise the impact of any side effects you may have.

Some of the most common side effects related to treatment (GEM/CIS/DURVA)

Hematotoxicity: side effects on your blood cells including

- **Low number of white blood cells and risk of infection**

White blood cells protect you against infections. If your white blood cell count is too low (this is called *neutropenia*) you may be at risk of infections. At this time, it is important to be careful to avoid situations that could increase this risk of infections, such as being in crowded places or in touch with people with colds.

The number of your white cells is most likely to be at its lowest between day 10 and day 14 of each of the cycles of treatment. Therefore, during these days it is important to avoid any risks of infection.

Reduction in white blood cells will be checked before every further cycle to ensure that the number of white blood cells is enough to protect from infection while receiving treatment.

It is important to be aware of the signs and symptoms of infection, and you must contact the helpline at your hospital if you develop any of the following:

- Your body temperature rises above 38°C (100.4°F), despite using paracetamol
- You suddenly feel shivery or unwell
- You develop a sore throat, a cough, diarrhoea, increased frequency of urination

- **Low number of red blood cells**

Red blood cells normally carry oxygen to every part of your body. If the number of red blood cells is too low (this is called *anaemia*) you can feel tired and breathless. If the *anaemia* is severe, you will need a blood transfusion.

- **Low number of platelets and risk of bruising or bleeding**

Platelets are useful to help the blood clotting.

If your number of platelets is too low (this is called *thrombocytopenia*) your doctor will delay your treatment until the platelet count improves. If you have any bruising or bleeding, such as nosebleeds, bleeding gums, tiny red or purple spots on the skin, please inform your doctor.

Flu-like symptoms: you may experience these during treatment or shortly after:

- Feeling hot, cold or shivery
- Fever
- Headache
- Muscle pain
- Fatigue

Blood clotting: contact the helpline if your legs are swollen, red and sore or if you develop breathlessness.

Diarrhoea and colitis: you need to get in touch with your doctor or nurse if you have 4 or more loose poos (stools) in 24 hours, wake up at night to pass stools or if you see blood and/or mucus in your stool. Your doctor will give you anti-diarrhoea medicines. Remember to drink plenty of water to replace fluids lost. If you have diarrhoea you should eat low-fibre food and avoid raw fruits, fruit juice, cereals and vegetables. It can help to also avoid alcohol, caffeine, dairy products and high-fat-foods.

Nausea: sometimes accompanied by vomiting but is usually well controlled by anti-sickness drugs (injections and tablets). You can experience it from a few hours to a few days after treatment. It is important to take anti-sickness medicines even if you don't feel sick, because it is easier to prevent sickness rather than treat it once it has started. Contact your doctor or nurse straight away if you've been feeling sick more than once in a day.

Skin toxicity: it includes rash, itching, patches of paler skin. It is important to protect your skin with a sun cream with a high protection factor. Rarely, immunotherapy can cause a serious skin condition with rash and blisters. In this case, please contact your hospital team.

Kidney damage (nephrotoxicity): this treatment can be harmful for kidneys, especially if you already have an underlying renal impairment. You will have blood tests before treatment to check how well your kidneys are working. Your doctor will discuss with you and will decide the best dose of chemotherapy for you in order to avoid further kidney damage. To help prevent damage, it is important to drink plenty of water. Your nurse might ask you to keep a record of how much you drink and of the amount of urine that you pass. Tell your doctor if you notice any changes in your urine, for example the presence of blood.

Hearing changes (ototoxicity): you might notice a ringing sound in your ears, called *tinnitus*. This often gets better on its own once the treatment ends. Rarely, it could be persistent for a long time after treatment ends. Let your doctor or nurse know if you notice any changes in your hearing.

Hormone changes: the most frequent alteration involves thyroid gland hormones. In case of low thyroid gland hormones, you may feel tired, have cold sensitivity or you may gain weight; in case of high thyroid gland hormones, you may feel nervous and anxious, and you may lose weight with no reason. Other possible symptoms related to hormonal dysregulation include increased sweating, dizziness, loss of sex drive, peeing more than usual, feeling more hungry or thirsty than usual, have headaches, feeling tired. Your hormone levels will be checked before each cycle.

Liver toxicity: sometimes the alteration of how liver works can become serious. You must contact your doctor or nurse if you have yellow skin or eyes, feel sleepy, have dark urine and pale stool, have unexplained bleeding or bruising. Your liver function will be checked before each cycle.

Build-up of fluid: You may put on weight and your face, or your ankles or legs may swell. It can help to put your legs up on a cushion. The swelling will get better after the end of treatment.

Fatigue: a very common side effect, which may increase during the treatment course.

For any of these toxicities, you may need steroids or other specific treatment.

Some less common side effects related to treatment (GEM/CIS/DURVA)

Allergic reaction: sometimes this happens while treatment is given. Tell your doctor or nurse immediately if you have any of these sudden symptoms:

- rash
- shortness of breath
- redness or swelling of the face
- feeling hot
- dizziness
- need to pass urine

Numbness or tingling in fingers and toes (peripheral neuropathy): cisplatin-based chemotherapy can affect nerves by causing numbness, tingling or pain in the hands or feet. Numbness or tingling in fingers and toes can make it difficult to do fiddly things such as tying your shoelaces or doing up buttons. This might start within a few days or weeks and last for a few months. Rarely, the numbness may be permanent. You can find specific tips below to help to reduce these symptoms if they occur.

Lung inflammation or pneumonia: please contact your doctor or nurse in case of breathlessness, cough, wheezing or fever with a temperature over 38°C (100.4°F), despite paracetamol.

Poor appetite: don't worry if you don't eat much for a day or two. Also, your taste can change. It is important to take small sips of fluids and try to eat small amounts often.

Extravasation (leakage) of infusional treatment: While it is being administered, chemotherapy and immunotherapy can sometimes leak outside the vein and damage the tissue around. Tell your nurse immediately if you have any stinging, pain, redness, or swelling around the vein.

Constipation: eating high-fibre foods (vegetables, fruit, wholemeal bread) and drinking at least 2 litres of water can help you. You may need laxatives if it lasts for longer than two/three days.

Mouth sores, ulcers, and candidiasis: you need to brush your teeth every time after eating to avoid germs growing. Use a soft toothbrush and rinse three times a day with 1/2 to 1 teaspoon of baking soda mixed in water. It's better to avoid acidic foods such as oranges, lemons and grapefruits; tell your doctor or nurse if you have ulcers, as they can help to prevent or to treat mouth sores. The most common mouth infection is called candidiasis and it shows as white spots on your mouth and tongue, which can also appear red and swollen.

Heart toxicity: this treatment can affect how the heart works and you may have tests to see how your heart is working.

It is important to be aware of the signs and symptoms of a potential heart problem, and you must contact the helpline at your hospital if you develop any of the following:

- chest pain or tightness
- breathlessness
- dizziness
- changes in your heartbeat

Muscle and joint pain: sore or weak muscles, sore or swollen joints.

Drowsiness: treatment may cause you to feel very sleepy (drowsy) and tired. If you feel very sleepy, do not drive or operate machinery.

Headache: if this happens, you may take painkillers like paracetamol.

Difficulty in sleeping: you can take sleeping tablets if you need them.

Hair loss: your hair may get thinner, but it is unlikely that you will lose your hair.

Raised blood sugar levels: please report to your doctor or nurse if you feel thirstier, need to pee more often or feel tired. If you already have diabetes your blood sugar levels may be higher than usual.

Medication to help control side effects

Make sure to let your doctor know of any side effects; there are useful medications to control the symptoms.

Should I continue to take all my usual medications?

Yes, you have to keep taking all your usual medications. Please report to your oncology team all the medications you are taking, so that they can advise.

Can I have the flu and COVID vaccination?

Yes, it is advised you have the flu and COVID vaccination before you start your treatment. If you have already started your treatment, please ask your doctor who can advise on the best timing to have the vaccination.

Tips during treatment

- Drink plenty of fluids (at least 2 litres per day).
- Maintain good nutrition. Eating small frequent meals may help to reduce nausea. You should avoid fatty or fried foods. You can take anti-sickness drugs if you need.
- Avoid sun exposure. Wear SPF 15 (or higher) sunblock and protective clothing.
- Get plenty of rest.
- To prevent or minimize numbness and tingling:
 - avoid exposing your hands or feet to lower temperature. This can be helped by using gloves when you go for a walk in winter or by not touching frozen food/drink. Use oven gloves when cooking and protective gloves when gardening
 - keep your hands and feet warm, wear well fitting, protective shoes
 - take care when using hot water as you may not be able to feel how hot it is and could burn yourself
 - take care when cutting your nails
 - moisturise your skin at least a couple of times a day
- Keep at home the medications you may need to help control the symptoms.
- You may experience drowsiness or dizziness; avoid driving or engaging in tasks that require alertness until your response to treatment is known.
- Use an electric razor when shaving and a soft toothbrush to minimize bleeding.
- Before starting treatment, tell your doctor about any medication you are taking. Sometimes side effects may be related to your medicines and not to chemotherapy.
- If your symptoms are severe or do not improve after 24 hours, do not hesitate to contact the hospital. Pay attention to symptoms of a blood clot: pain, redness, swelling of an arm or a leg, breathlessness or chest pain. If you have any of these symptoms contact your doctor.
- Do not receive any kind of vaccination without your doctor's approval while having your treatment.
- If you are a woman of childbearing age:
 - inform your doctor if you are pregnant or may be pregnant prior to starting this treatment
 - avoid getting pregnant during treatment
 - do not breastfeed during treatment

When to contact the hospital?

If your symptoms are severe or do not improve after 24 hours, do not hesitate to contact the hospital.

Where can I get more information?

If you want to get more information in this field you can visit **ESMO** website for *Biliary tract cancer: Guide for Patients* and on the **AMMF** *The Cholangiocarcinoma Charity* website.

You can find the related link below:

<https://www.esmo.org/for-patients/patient-guides/biliary-tract-cancer>

<https://ammf.org.uk/cholangiocarcinoma/>

You can also visit the Precision-BTC-Network COST action website:

<https://precision-btc.eu/info/patientmaterials>