Digestive Cancers Europe

Advanced Gastric Cancer Educational Booklet

A guide to help you and your carer make informed choices on your testing and treatment



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Prologue

There are many challenges that come with being diagnosed with advanced gastric cancer. It is daunting to pay attention to all the tests, treatments, and strategies that your doctors talk about, while internally your world is spinning out of control.

Also, there is a lot of information available at the touch of a button, but it is important not to go headfirst comparing cases, looking for statistics, and trying to find all the answers. You will be overwhelmed and spiral out of control with the wrong influence. This booklet takes some of the hard truths and explains them in a simple manner.



I was just starting my adult life, as a young

architect, when I was diagnosed at 23, with stage 4 gastric cancer. Like many, I was diagnosed once the disease was advanced. I was lucky to have my girlfriend and mother's support as I processed my diagnosis on my terms. They were the ones who did the research on testing and the best lines of treatment for me, they made my transition into treatment smooth and took a huge burden off my shoulders.

Not everyone has such a support system, which is why I believe the scope of this booklet is informative without being scientifically challenging to patients and carers. It highlights many of the topics that are important to understand while navigating testing and treatments.

My journey has been challenging, but I am grateful for the incredible support of my family and friends as I continue to fight on! I have uprooted my life in Romania and I am currently enrolled in a clinical trial in the US, hoping to benefit from a novel drug combination therapy.

This educational booklet developed by Digestive Cancers Europe will be a nice companion to patients, and their carers, as they navigate testing and treatment. I hope this booklet will empower patients and carers to have important conversations with their care teams on all aspects – from diagnosis to treatments, well-being, and making difficult decisions.

George Vasiliu,

Advanced Gastric Cancer Patient

About this educational booklet

We understand that receiving a diagnosis of advanced gastric cancer or being told that your cancer has spread (metastasized) can be confusing and overwhelming. We have created this booklet together with clinicians, scientists, medical writers, and gastric cancer patients, to help you through the challenges that you may encounter. We hope to help to inform, educate, and empower you to understand the testing and treatment options for your diagnosis.

This booklet will guide you through:

- Your advanced gastric cancer diagnosis
- Testing that may be offered
- Possible treatment options and what you may experience

After reading this booklet, we hope that you will feel more comfortable and confident about:

- Asking questions about your testing and treatment
- Having open conversations with your care team
- Explaining your testing and treatment to your loved ones



Your journey with advanced gastric cancer

Who is on your team?

You are not alone with your diagnosis of advanced gastric cancer. You will have a care team that will help you on your journey, as well as your family and friends.



Gastric cancer requires expert care, so your care team will include your oncologist, surgeon, pathologist, radiotherapist, nurses, and experts including dietitians, pharmacists, primary care physicians, social workers, counselors, therapists, psychiatrists, insurance, financial advisors, etc.

They are available to answer your questions, give you suggestions, and provide you with overall support.

How are testing and treatment decisions made?

Your care team's goal is to support you, while explaining and informing you about all your options. You are the center of a personalized decision-making process.

How deeply involved you are in this process is completely your choice.

What is important is that you do what feels right for you; this can include expressing your opinions and asking questions about testing procedures, treatment approaches, your changing symptoms, as well as feelings and emotions surrounding your diagnosis.



What is gastric cancer?

Gastric cancer is a cancer of the stomach. When cells in the stomach begin to behave abnormally, they can turn cancerous and grow out of control. This can prevent the stomach from working properly, causing uncomfortable symptoms. Sometimes these symptoms may be overlooked, and the cancer is only diagnosed once it has spread.

A diagnosis of advanced gastric cancer means that the cancer that originated in your stomach has spread to other locations in the body. Advanced gastric cancer most often spreads to the lungs, liver, lymph nodes, peritoneum (tissue that covers the organs in your abdomen) and bones.

Advanced Gastric Cancer

Locally advanced gastric cancer: cancer that has spread to nearby tissues or lymph nodes.

Metastatic gastric cancer: cancer that has spread (metastasized) to at least one other organ, or distant parts of the body.

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Risk factors

Your family members should be aware of inherited risks in order to make changes that can reduce these risk factors. It is well established that healthy lifestyle habits and early diagnosis can reduce the occurrence of gastric cancer, this can be valuable knowledge for a loved one.¹



1. Correa, P. Gastric Cancer. Overview. Gastroenterology Clinics of North America vol. 42 211-217 (2013).

Diagnosing and staging your advanced gastric cancer

To establish the precise stage of your cancer, and personalize your treatment, you will undergo a series of tests and evaluations. These tests can include endoscopies, biopsies, lab tests and imaging scans.²

Your care team may stage your gastric cancer at different times throughout your testing and treatment.

Stage I

The earliest stage, when the cancer is localized to the lining and connective tissues of the stomach.

Stage II

The cancer has grown through the lining of the stomach and into the thick inner muscles of the stomach.

Most advanced gastric cancers are classified under:

Stage III The

The cancer has spread and grown into or through the layers of your stomach. The cancer may have also spread to nearby lymph nodes, but it has not spread to other organs.

Stage IV The cancer has infiltrated the nearby tissues and organs or has now spread across your body.

The TNM staging system can be complex, we have created a simplified illustration to outline the **4 stages**.

Your oncologist will utilize the TNM staging system (tumor (T), nodes (N) and level of metastasis (M)) to determine the stage of your cancer.



Staging of gastric cancer can be complex and overwhelming to understand. If you are unclear about the staging of your advanced gastric cancer, ask your care team to explain using visuals and models.

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2. Smyth, E. C. et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27, v38–v49 (2016).

Testing for advanced gastric cancer

Pre-existing medical conditions, other health concerns, and the staging of your gastric cancer, will guide your care team's recommendation for molecular diagnostics to better understand the characteristics unique to your cancer.

Biomarkers of gastric cancer

Biological markers or "biomarkers" are biological molecules present in your blood and in other bodily fluids or tissues. They indicate signs of normal or abnormal processes, or a disease state. Biomarkers can be a change (also known as a mutation) in your DNA, RNA, or protein.^{3,4}

Biomarkers can be measured in your blood, tissues and other bodily fluids and can provide specific and detailed information about individual changes unique to your disease profile.⁴

Biomarker testing can provide information that helps:

- Determine your risk of developing a cancer
- Determine your cancer characteristics (subtype)
- Determine the aggressiveness of your cancer
- Predict how your body will respond to treatments
- Determine how your cancer is likely to progress

Biomarkers function differently in different cancer types. If you have recently been diagnosed with advanced gastric cancer or your gastric cancer has metastasized, your care team should have already started discussing comprehensive biomarker testing with you.

If there is suspicion of hereditary disease, there are biomarker tests that your team will suggest to assess inherited genetic changes that can be passed down to you from your family.^{5,6} Your family may be directly affected if your testing results conclude that your cancer originated from inherited mutations. Should this be the case, you may be recommended to speak with a genetic counsellor to better understand how your test results may impact you and your family.

Identifying the biomarkers unique to your advanced gastric cancer will allow your care team to inform you about all your therapeutic options, which will allow you and your family to be better informed in the decision-making process.



^{3.} Henry, N. L. & Hayes, D. F. Cancer biomarkers. Molecular Oncology vol. 6 140–146

Preprint at https://doi.org/10.1016/j.molonc.2012.01.010 (2012).

Matsuoka, T. & Yashiro, M. Biomarkers of gastric cancer: Current topics and future perspective. World Journal of Gastroenterology vol. 24 2818–2832 (2018).

^{5.} Herrera-Pariente, C. et al. Biomarkers for gastric cancer screening and early diagnosis. Biomedicines vol. 9 (2021).

Stjepanovic, N. et al. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology vol. 30 1558–1571 (2019).

Why are biomarker tests used for selecting treatments for advanced gastric cancer?

Several treatments for advanced gastric cancer, including immunotherapy or targeted therapies, only work for cancers that have specific biomarkers.

By testing for these biomarkers, your care team can tailor a specific therapy regimen for you, this is known as precision medicine or personalized medicine.^{5,7}

It is important to note, that even if your cancer tests positive for certain biomarkers, it is not guaranteed that the relevant targeted molecular therapies will work seamlessly. This is because the molecular makeup of your cancer cells may evolve over time, and your cancer may continue to develop, meaning that the targeted biomarkers may change.

Should you become resistant to a targeted therapy, your team may suggest retesting some of your biomarkers to understand the changes, and to identify new biomarkers for targeted treatments.



Precision medicine focuses on finding treatments that are most likely to benefit your cancer profile while avoiding treatments that are not likely to help.

It is important to recognize that extensive biomarker testing and profiling may not be available in all medical institutions across Europe. Current guidelines recommend that biomarker testing is done at the time of initial diagnosis for patients with advanced gastric cancer.²

However, this may not be a testing option available at all medical institutions. Therefore, it is important for you and your carer to openly discuss all your testing options with your care team, to understand them and ask for clarification when needed, during your initial appointments.





The Testing Process

Biomarker testing requires a sample of your cancer cells, these may be collected during surgery.

If you are not having surgery, you may have a biopsy of your tumor(s). Biopsies of the stomach rely on the use of upper endoscopy and involves removing a small piece of your tumor(s) for further analysis.

In some cases, a liquid biopsy may be performed if your tumor is in a hard-to-reach position. This can include sampling blood, gastric juices, or other bodily fluids of relevance to your tumors by assessing the circulating DNA (genetic information) shed from tumors.

Liquid biopsies are not yet standard practice for all cancer types and in all treatment centers across Europe, but you can always discuss whether liquid biopsies might be used for periodic testing of your advanced gastric cancer with your care team.



Once collected, your sample(s) will be sent to an experienced, centralised laboratory where they will be tested for specific biomarkers associated with gastric cancer, using validated tests and interpreted by accredited pathologists.

Your care team will receive a detailed report and they will explain and discuss the results in detail with you.

Learning about the results of your biomarker testing may be confusing and overwhelming.

If you still have questions, you could ask for a copy of your results and review them in the comfort of your home, with your carer. We have suggested some questions on page 26 which you can make note of to discuss during a follow-up visit with your care team.



Biomarkers of advanced gastric cancer

Biomarker testing is part of standard care for many types of cancer, and can be particularly helpful in designing a targeted treatment approach. The most common biomarkers for gastric cancer include:

HER2

Human Epidermal Growth receptor 2 (HER2) is a protein involved in growth, division, repair, and survival, and is found in small amounts in all human cells.

Sometimes a random change within gastric tumor cells can result in too many copies, or over-expression of HER2. This can cause the cancer cells to grow and spread into organs across the body (metastasis) and is associated with poor prognosis and overall outcomes. HER2 is overexpressed in ~20% (2, -) of gastric cancers, making the HER2 pathway

making the HER2 pathway an important biomarker and therapeutic target for gastric cancer.^{8,9,20}



ESMO 2022 Guidelines recommend recommend testing the HER2 status of all patients with advanced gastric at the time of their initial diagnosis.

Gastric cancer progresses rapidly and since most patients present with advanced disease it is recommended that diagnostic turnaround time for HER2 should be within 5 working days, however this may take longer at some institutions.²

Diagnosis should be made from multiple (5-8) endoscopic biopsies, as it is possible that a single sample may not have HER2 positive (HER2+) cells.

Samples should be validated in a centralized testing center by a trained and experienced pathologist.

Your care team will receive a detailed pathology report. If you are HER2+, they will discuss the HER2 targeted therapy treatment options best suitable for you.

^{2.} Smyth, E. C. et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27, v38–v49 (2016).

Iqbal, N. & Iqbal, N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. Molecular Biology International 2014, 1–9 (2014).

Gunturu, K. S., Woo, Y., Beaubier, N., Remotti, H. E. & Saif, M. W. Gastric cancer and trastuzumab: First biologic therapy in gastric cancer. Therapeutic Advances in Medical Oncology vol. 5 143–151 (2013).

van Cutsem, E. et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 18, 476–484 (2015).

VEGF

As tumors grow, they create new blood vessel networks to bring in blood, nutrients, and oxygen. This expansion is called angiogenesis, a hallmark of metastatic gastric cancer, and key proteins involved in the building of blood vessels are Vascular Endothelial Growth Factors (VEGFs).¹⁰ Testing for VEGFs and their respective receptors (VEGFrs) will allow your care team to understand how your tumor(s) sustain their growth and the best approach to cutting off your tumors from their energy supplies.

PD-L1

Your body's immune system knows it must attack foreign invaders such as viruses and bacteria but not your own healthy cells. One protein that helps your immune system to recognize non-harmful cells is called programmed death ligand 1 (PD-L1). However, with some cancer types such as gastric cancer, the cancer cells produce a high amount of PD-L1 which can evade the immune system. Testing your tumor cells PD-L1 levels will enable your care team to consider immunotherapy options for your treatment.

CDH1

1% to 3% of stomach cancers are hereditary diffuse gastric cancers (HDGC). If you have a known family history of gastric cancer or lobular breast cancer, your doctor will want to test several genes known to be passed down with changes (mutations) that might have increased your cancer risk. CDH1 is the gene that is commonly associated with HDGC, and a change in this gene can increase your risk for gastric cancer. Your doctor may suggest further genetic testing and genetic counselling to help you and your family to understand your results.

BRCA1 & BRCA2

While most commonly associated with hereditary breast and ovarian cancers, BRCA mutations have been associated with an increased lifetime risk of developing gastric cancer among first degree relatives of BRCA 1 and 2 mutation carriers. These two tumor suppressor genes play roles in DNA repair, cell growth and cell death processes.^{11,12} Mutations in these genes can lead to DNA damage and tumor development. Similarly, to CDH1 testing, your doctor may suggest genetic tests and counselling to help you and your family understand your results.

Although there are several valuable biomarkers for advanced gastric cancer, your care team will evaluate the best testing strategy, which may include a combination of different biomarkers, and clinical and biochemical parameters to make the best diagnosis.



Forma, A., Tyczyńska, M., Kędzierawski, P., Gietka, K. & Sitarz, M. Gastric carcinogenesis: a comprehensive review of the angiogenic pathways. Clinical Journal of Gastroenterology vol. 14 14–25 (2021).

Cavanagh, H. & Rogers, K. M. A. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hereditary Cancer in Clinical Practice vol. 13 (2015).

Maccaroni, E. et al. BRCA mutations and gastrointestinal cancers: When to expect the unexpected? World Journal of Clinical Oncology 12, 565–580 (2021).

Other diagnostic methodologies for advanced gastric cancer

In addition to biomarkers, the inclusion of several other testing methodologies may be considered, in order to have a better overview of your advanced gastric cancer, for designing and optimising your treatment.



Tumor mutational burden (TMB)

Your care team maybe be interested in assessing your tumor mutational burden (TMB), because it highlights the number of mutations (changes) that have occurred in the DNA of your cancer cells. Tumors that have a high number of mutations or a high TMB, seem to respond better to certain types of immunotherapies and this may provide valuable

information about your gastric cancer.



Microsatellite Instability (MSI)

We all have major mismatch repair (MMR) genes which play an important role in repairing DNA but sometimes, they do not function as they should.

Looking at the stability of parts of the DNA called microsatellites will allow your care team to assess if these MMR genes are working properly. Knowing if your cells have a high level of microsatellite instability (MSI-H), or a change or defect in a mismatch repair protein (dMMR) will guide your care team to evaluate immunotherapy as a possible treatment, and could warrant further evaluation for Lynch Syndrome. Lynch Syndrome is a hereditary predisposition to several cancer types including gastric cancer.¹³



Next Generation Sequencing (NGS)

NGS is not a biomarker, rather it is a valuable diagnostic test that provides an overview of changes across a number of genes simultaneously; allowing insight into a variety of genetic biomarkers and a deeper understanding of your cancer using a tissue or blood sample.

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Compared to individualized traditional testing methods, NGS assesses multiple genes in a single test, with accuracy and sensitivity. This reduces the need to be subjected to multiple tests in order for your team to identify the cause of your cancer mutations, and decide on targeted therapies for your specific cancer profile.

Some hospitals perform NGS as part of the initial cancer screening process. As it is an expensive screening tool, other medical institution may rely on it when standard treatments do not seem to be working for your gastric cancer.

Your care team may or may not recommend these diagnostics, however they may consider them in the event of a new metastasis or progression of your disease.

13. Boland, C. R., Yurgelun, M. B., Mraz, K. A. & Boland, P. M. Managing gastric cancer risk in lynch syndrome: controversies and recommendations. Familial Cancer vol. 21 75-78 (2022).

Treatment options for advanced gastric cancer

Once testing has been conducted, and your results have been evaluated, it is time for your treatment to be planned. Treatment of gastric cancer is primarily influenced by where the tumor originated and how widely it has spread.

Other factors, such as your overall health, age, and personal preferences, are also important in the decision-making process. Treatment planning should involve the expertise of your care team which consists of multidisciplinary members, with everyone working together towards the best possible outcome for you.

Current therapies used for localised advanced gastric cancer include:



SURGERY



IMMUNOTHERAPY



CHEMOTHERAPY

RADIOTHERAPY



TARGETED THERAPIES

- HER2-targeted therapies
- Anti-angiogenesis therapies
- TRK-targeted therapies

The types of therapies used for inoperable advanced and metastatic gastric cancer include:



PALLIATIVE CHEMOTHERAPY



ENROLMENT IN A CLINICAL TRIAL



TARGETED- AND IMMUNO- THERAPIES

BEST SUPPORTIVE CARE IF UNFIT FOR TREATMENT

There is one common goal for all lines of treatment of advanced gastric cancer: to extend survival and control the clinical symptoms of the disease while keeping toxicity levels low and quality-of-life as high as possible.^{14,15}

 Hu, H. M. et al. Survival outcomes of management in metastatic gastric adenocarcinoma patients. Scientific Reports 11, (2021).
 Pellino, A. et al. Targeted therapies in metastatic gastric cancer: Current knowledge and future perspectives. World Journal of Gastroenterology vol. 25 5773–5788 (2019).





Treating unresectable locally advanced gastric cancers

Unresectable local gastric cancers refer to cancers that have not spread to other parts of the body, but due to their location, they cannot be fully resected, or surgically removed.

Your care team will possibly recommend one of the following, as a first line of treatment:

- Chemotherapy alone
- Chemotherapy with radiation therapy
- Chemotherapy combined with immunotherapy, or targeted therapy
- Chemotherapy combined with immunotherapy plus a targeted therapy

How you respond to treatment will be thoroughly evaluated to assess whether your tumor or tumors are shrinking or have stopped growing. If your cancer has responded positively and has shrunk, surgery to remove the tumor may become possible. Alternatively, your surgeon may recommend removing part or all of your stomach, lymph nodes and other affected tissue and organs. They will explain the procedure in detail, and what it means to recover after such a surgery.

If the cancer remains inoperable following a first line of treatment, and the tumor(s) continue to grow despite treatment, the next treatment will also aim at repressing the tumor growth and relieving your symptoms.



Metastatic cancers

This type of stomach cancer is difficult to cure because it has spread to the far reaches of the body.

Treatment can help control the growth, and relieve uncomfortable symptoms, with the aim to maintain a comfortable quality of life.

Your care team will possibly recommend either of the following:

Chemotherapy alone Chemotherapy with radiation therapy; if you are healthy enough to tolerate the side effects

Chemotherapy combined with immunotherapy, or targeted therapy Chemotherapy combined with immunotherapy plus a targeted therapy

Different people will respond differently to each treatment and your team might need to try several different drugs and combinations to find an effective treatment for you.





Surgery

If your gastric cancer is operable this may involve removal of the cancer itself, and part - or all of the stomach as part of your curative treatment. Lymph nodes in close proximity may also be removed, as well as other organs, depending on how far the cancer has spread.

The goal of surgery is to remove all the cancer when possible, while conserving the neighboring healthy tissue and organs.

Surgery to prevent the tumor from growing and blocking the stomach, or to relieve painful symptoms caused directly by the growing tumor, is referred to as palliative surgery.

Most often when gastric cancer metastisizes it tends to spread into other organs, making it in-operable.



Chemotherapy

Chemotherapy refers to drugs to enter your bloodstream and disperse to all parts of your body and take effect, especially if the cancer has spread or metastasized.

Chemotherapy is usually prescribed in cycles; with a timeframe of several weeks for treatment followed by a rest and recovery period of a few weeks. It can be used in different ways and at different times based on the stage and type of your gastric cancer. Chemotherapy can help slow down or shrink a tumor, thereby alleviating pain and pressure caused by large tumors.

Chemotherapy for gastric cancer:

- The detailed testing of your specific cancer and your overall health status will allow your care team to choose the right treatment combination for you.
- There are several different chemotherapy drugs, and it is common to receive a combination of several of these drugs.
- It is most common, for patients with advanced gastric cancer, to start treatment with a combination of 2 drug therapies to reduce the burden of side effects.

Chemotherapy can have side effects on the body and mind that can be unpleasant and difficult to manage. We have listed some of the side-effects associated with chemotherapy in the Table on PG 21.





Radiation Therapy

Radiation therapy, sometimes referred to as radiotherapy, utilizes high doses of energy rays or particles to kill cancer cells or shrink tumors in specific

As most advanced gastric cancers are inoperable, radiation therapy can work to slow down the growth of tumors and alleviate uncomfortable and painful

of tumors and alleviate uncomfortable and painful symptoms, including bleeding and discomfort when eating.

For tumors in the stomach, the radiation is focused on the abdomen area through a machine. A computer is used to target the beams on the tumor at the most efficient angles so that it preserves healthy surrounding tissue.

Prior to starting your radiation therapy, your care team will conduct measurements to determine the correct angles and doses, using imaging tests such as CT and MRI scans.

Radiation treatments are usually scheduled for several days in row, over several weeks. The treatment itself lasts just a few minutes and while painless, you may experience side effects after treatment. We have listed some of the side-effects associated with radiation in the Table on PG 21.

When radiation therapy is combined with other treatments, the side effects might be more severe and unpleasant although most types of pain and discomfort tend to go away or become less between treatments. However, the nerve damage tends to get worse after each treatment; and this discomfort is slow to subside and heal.





Every treatment may cause you to have symptoms, it is important to keep track of your symptoms and share them with your care team, they may be able to help you alleviate some discomfort through dietary modifications, physical therapy, or other medications.

Some of these symptoms should subside once treatment has been completed. However, always discuss any questions or concerns you may have with your medical team.



Targeted Therapies for advanced gastric cancer

Advancements in research and development, and positive results from clinical trials, has led to new drugs that can target specific molecules in certain types of cancer, including gastric cancer.

These drugs aim to inhibit the growth and spread of cancer cells, while limiting damage and destruction of healthy cells. Targeted therapy drugs may work when chemotherapy drugs do not, or they may be combined with chemotherapy and radiation therapy.

Monoclonal Antibody treatments

Monoclonal antibodies are molecules engineered and produced in a laboratory to work with your body's natural defences, your immune system, to stimulate the body's attack on cells they are meant to target, such as cancer cells.

Several monoclonal antibody work as inhibitor target therapies for biomarkers of advanced gastric cancers.

HER2 targets: Trastuzumab & Fam-trastuzumab Deruxtecan

After testing, you and your care team should know the HER2 status of your gastric cancer. For some people with stomach cancer, the surface of the tumor cells may have too much of the protein HER2. Having increased HER2 levels is categorized as HER2 positive (HER2+). Currently, there are several European Medical Agency (EMA) approved drugs that target the HER2 protein.





Trastuzumab

This targeted therapy is a monoclonal antibody that is used to treat HER2+ gastric cancers. This means that the drug can only be used if your cancer produces too much HER2, which occurs in about 20% of gastric cancers.

Trastuzumab can be delivered either through an IV into a vein, via a central venous catheter or subcutaneously. It is typically combined with chemotherapy for 2 to 3 weeks.⁹

Studies have shown that HER2+ gastric patients may have a greater benefit of life expectancy from a combination of trastuzumab and chemotherapy, than chemotherapy alone.

Side effects of Trastuzumab alone might be mild in comparison to its use in combination with other therapies.

Trastuzumab is available in the form of an originator drug as well as in a form of a biosimilar medicine. Biosimilar medicines or biosimilars are biological medicines that contain essentially the same active substance as their originator. Although minor differences may exist, a biosimilar matches the originator in terms of quality, safety and efficacy, and is approved by the EMA.

We have listed some of the side-effects associated with Trastuzumab in the Table on PG 21.

Fam-trastuzumab Deruxtecan

This is a monoclonal antibody that is conjugated or connected with a chemotherapy drug known as an antibody drug conjugate (ADC). This approach may be considered after first-line chemotherapy with Trastuzumab once it does not seem to be working. The drug is delivered via an IV into a vein or via a central venous catheter and is administered once every 3 weeks. The Trastuzumab antibody attaches to the HER2 proteins on the cancer cells and brings the chemotherapy drugs straight to them.

You can expect similar side-effects as associated with Trastuzumab for Fam-trastuzumab Deruxtecan as described in the Table on PG 21.

VEGF Target: Ramucirumab

This drug is also a monoclonal antibody, and its target is the VEGF receptor.

Ramucirumab blocks VEGF from binding to cells and stops the expansion of blood vessels, thereby cutting off the tumor's nutrients and blood supply. It can stop or slow down the growth of some gastric tumors.

Ramucirumab is delivered via an IV into a vein or via a central venous catheter and is administered once every 2 weeks.

Your care team may suggest trying Ramucirumab if the first line chemotherapy drug(s) stop working or it may be combined with another chemotherapy drug.

We have listed some of the side-effects associated with Ramucirumab in the Table on PG 21.

^{9.} Gunturu, K. S., Woo, Y., Beaubier, N., Remotti, H. E. & Saif, M. W. Gastric cancer and trastuzumab: First biologic therapy in gastric cancer. Therapeutic Advances in Medical Oncology vol. 5 143–151 (2013).

Immunotherapy

Like targeted therapies, modern research and technology have led to the development of immunotherapy medicines that work with your own immune system to fight and eliminate cancer cells efficiently.

One key characteristic of our immune system is that it must prevent itself from attacking and destroying normal and healthy cells in the body.

Checkpoint proteins are part of immune cells and they act as a brake to alert the immune system's response; turning it on or off. With certain types of cancers, the cancer cells utilize these checkpoints to go unnoticed and avoid being eliminated by the immune system.



PD-1 Targets: Nivolumab and Pembrolizumab

Both Nivolumab and Pembrolizumab EMA approved drugs that target the PD-1 protein. This protein is part of our T-cells, forming an important part of the immune system.

Both drugs block PD-1, allowing your immune system to cause a strong response against the cancer cells. Both drugs have been shown to help shrink slow the growth of stomach cancer tumors in patients with advanced disease.

Specifically, Nivolumab is typically used in combination with chemotherapy and is delivered via an IV into a vein or via a central venous catheter and is administered once every 2 to 3 weeks.¹⁶

Pembrolizumab is typically tried after a first line of chemotherapy, when tumors show a defect in a mismatch repair (MMR) gene or a high level of microsatellite instability (MSI-H) or a high tumor mutational burden (TMB); suggesting strong evidence of many gene mutations.

Like Nivolumab, Pembrolizumab is also administered via an IV into a vein or via a central venous catheter and is administered once every 3 to 6 weeks.¹⁷

We have listed some of the side-effects associated with Nivolumab and Pembrolizumab in the Table on PG 21.

16. Janjigian, Y. Y. et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. The Lancet 398, 27–40 (2021).

17. Janjigian, Y. Y. et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. The Lancet Oncology 21, 821–831 (2020).



Off-label treatment

Your team may suggest treatments that are currently not approved for your cancer but for other cancers that have a similar biomaker profile as your cancer.^{18,19}

This is known as off-label treatment. The recommendations are based on your team's knowledge and experience with the treatment, along with supporting research evidence that it may be useful for your stage and type of cancer. These treatments may work for your advanced gastric cancer because they target the same biomarkers.

Treatments and their known side effects

Chemotherapy	Radiation Therapy	Trastuzumab	Fam-Trastuzumab- deruxtecan	Ramucirumab	Nivolumab & Pembrozulimab
Nausea & vomiting	Nausea & vomiting	Nausea & vomiting	Nausea & vomiting	Diarrhea	Fatigue & weakness
Appetite loss	Skin peeling and blistering	Fever &/or chills	Fever &/or chills	Headaches	Constiption or diarrhea
Constipation or diarrhea	Low blood cell	Diarrhea	Constiption or diarrhea	pressure	Nausea &
Stomach pain	Stomach pain	Fatigue & weakness	Fatigue & weakness	Blood clots, cleeting	Appetite loss
Oral sores	Diarrhea	Headaches	Hair loss	Stomach and intestinal perforations	Skin rash / itching
Fatigue	Fatigue	Heart damage	Appetite loss	Poor wound	Fever
& bruising			Heart damage	healing	Coughing or trouble breathing
Shortness of breath			Lung disease		Muscle / joint pain
Hair loss					
Nerve damage					

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Considering a clinical trial as an option

Sometimes, when treatments have not worked and you choose to continue trying, a clinical trial might be an option.

Clinical trials offer experimental treatments; they come with benefits and risks, therefore it is important to have all your questions answered before you decide to enroll. It may be helpful to prepare a list of questions before you meet with your team; we have prepared some questions to get you started, you can find them at the end of this booklet.



Speak with your doctor about trials they consider right for your specific cancer type, stage, and location.

You can also search the internet for trials based on cancer type, type of trial, and trial location to find a match for your profile. Clinical trials have very specific guidelines and eligibility criteria that inform doctors on who can enroll, so it is important to speak with your care team to understand whether you would be a good fit.

Once you have found a clinical trial where you meet all the eligibility criteria, your doctor will assist you in enrolling as a participant. You will be additionally supported by the clinical trial team of doctors, researchers, and other medical professionals.



Choosing to stop treatment

Once on a trial, you can still make decisions about your treatment. If you decide that you would like to stop your cancer treatment, you should talk to your care team. At some point, you might consider hospice care.

The purpose of hospice care is not to treat your cancer but rather to improve your quality of life by relieving pain, and other symptoms caused by your advanced gastric cancer. It includes care of your physical, emotional, and spiritual well-being towards the end of life, and helps you and your loved ones maximize the time you have left.

Choosing to refuse treatment

After your diagnosis, your care team will present what they believe is the best and most appropriate treatment(s) based on your specific cancer profile and your overall health status. They will be available to answer all your questions, while easing your doubts, but you make the ultimate decisions regarding the choices for your care.

If you have advanced or metastatic gastric cancer that has not responded to treatments, or if you decide that comfort is of highest priority to you and your family, then you and your care team should work together to ensure that you are free of pain and that your symptoms are well managed.



Care through your final days

It is difficult to contemplate what to expect as you near the end of life – for you and your loved ones. Remember that it is important to openly discuss your choices with your care team. They will always be sympathetic to your needs.

If your gastric cancer has spread uncontrollably, chemotherapy and radiotherapy may be suggested by your care team as an option to improve your quality of life and extend your time with your loved ones.

Some surgical procedures may also be suggested to ease your symptoms and provide you with relief from pain and pressure caused by tumor(s).

Such interventions could include:

- Insertion of a feeding tube directly into the stomach to ensure appropriate nutritional uptake.
- Insertion of a stent to ease discomfort from blockage of the stomach.
- Cryotherapy to freeze away tumor tissue that might be obstructing the oesophagus or stomach, with the aid of endoscopy.
- Usage of internal radiation to kill cancer cells known as brachytherapy

Cancer can cause many forms of pain, and this can make it difficult for you to feel comfortable and at peace. Your care team can help with pain management; it may involve medications, massages and physical therapy, breathing and meditation techniques, acupuncture, heat or cold therapies, biofeedback therapies and nutritional counselling, just to name a few.



Finding support

All the testing and treatments surrounding your advanced gastric cancer can feel scary and intimidating.

We encourage you to consider reaching out to local patient organisations in order to find other patients who have been through the disease. Finding a support community for gastric cancer patients will allow you and your loved ones to connect with other patients and their families and share similar experiences, while relying on each other for support and comfort.

Your care team is a great resource to help you find a cancer support program for your specific type of cancer, in your own city. You can also do an online search for support groups using your diagnosis as a key search word followed by "support group" followed by the name of the "city" you live in.

Ways to keep track of your feelings

Self-reflection during this overwhelming time can help you stay in tune with how you are doing. One way to do it is through assessing your feelings. Make copies of this feeling assessment and circle the feelings and emotions you have experienced / are experiencing over the the last few days. Share this with your care team or psychologist or counsellor.



Ways to keep track of my side-effects

- Writing it down means you won't forget it, a journal can be a helpful place to start.
- Write down how you feel (emotionally and physically) before, during and after a treatment session.
- Share all the changes including new, painful and different side effects you have been experiencing. Monitoring your side effects helps your care team monitor your progress.
- If something is bothersome, share it immediately with your care team, so that they can help you manage your side effects as soon as possible.

Speaking with your care team to learn more

It is important for your to feel comfortable at all stages of your cancer treatment journey.

While it can be challenging to share how you have been feeling since you were last asked about it, remember that keeping an open and honest line of communication with your care team can give you the confidence and tools needed to stay informed about your over-all well-being, testing and treatments.

You should feel supported and free to ask any questions about your physical and emotional well being, your testing, treatments and side-effects.

Questions about my diagnosis

- What type of cancer do I have and where exactly is it located?
- What is the stage of my cancer?
- Has my cancer spread?
- What does this mean in terms of testing and treatment options?
- What is my prognosis?

Questions about testing

- What are my current testing options? Will be include biomarker testing?
- What biomarkers will we be testing for?
- What can biomarker testing tell us about my gastric cancer?
- Should we be thinking about genetic testing for my family?
- May I have a copy of my results?
- When would we consider re-testing some of my biomarkers?
- What are the limitations to biomarker testing?



Questions about treatment

- What are my best options for treatment?
- What are biologics and biosimilars?
- Will we combine several treatments? How does this normally work?
- How often will I need to come to the hospital/ clinic for treatment visits?
- How long does each treatment take?
- What happens during a treatment visit?
- How long does this treatment take?
- Can my partner/ carer stay with me during my treatment visits?
- How will I feel during each treatment visit?
- When should I expect to start feeling side-effects?
- How long are side-effects expected to last?
- Who can I contact after hours if I have questions about my side-effects?
- How will my side-effects be managed?
- What happens if my treatment does not work as expected?
- What if I cannot tolerate my treatment(s)?
- Who can I speak with about clinical trials?
- How do clinical trials work?

Questions about well-being

- How do I find emotional support through my diagnosis, testing and treatments?
- Is there emotional support available for my partner/ carer/ family?
- Is it normal to feel overwhelmed? How can I cope better?
- Can I be connected with patients like me, to support each other?
- Who can I contact after hours if I have questions about my emotional well-being
- Do I have access to a physical therapist?
- Do I have access to a nutritionist?



STIVE CANCERS

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