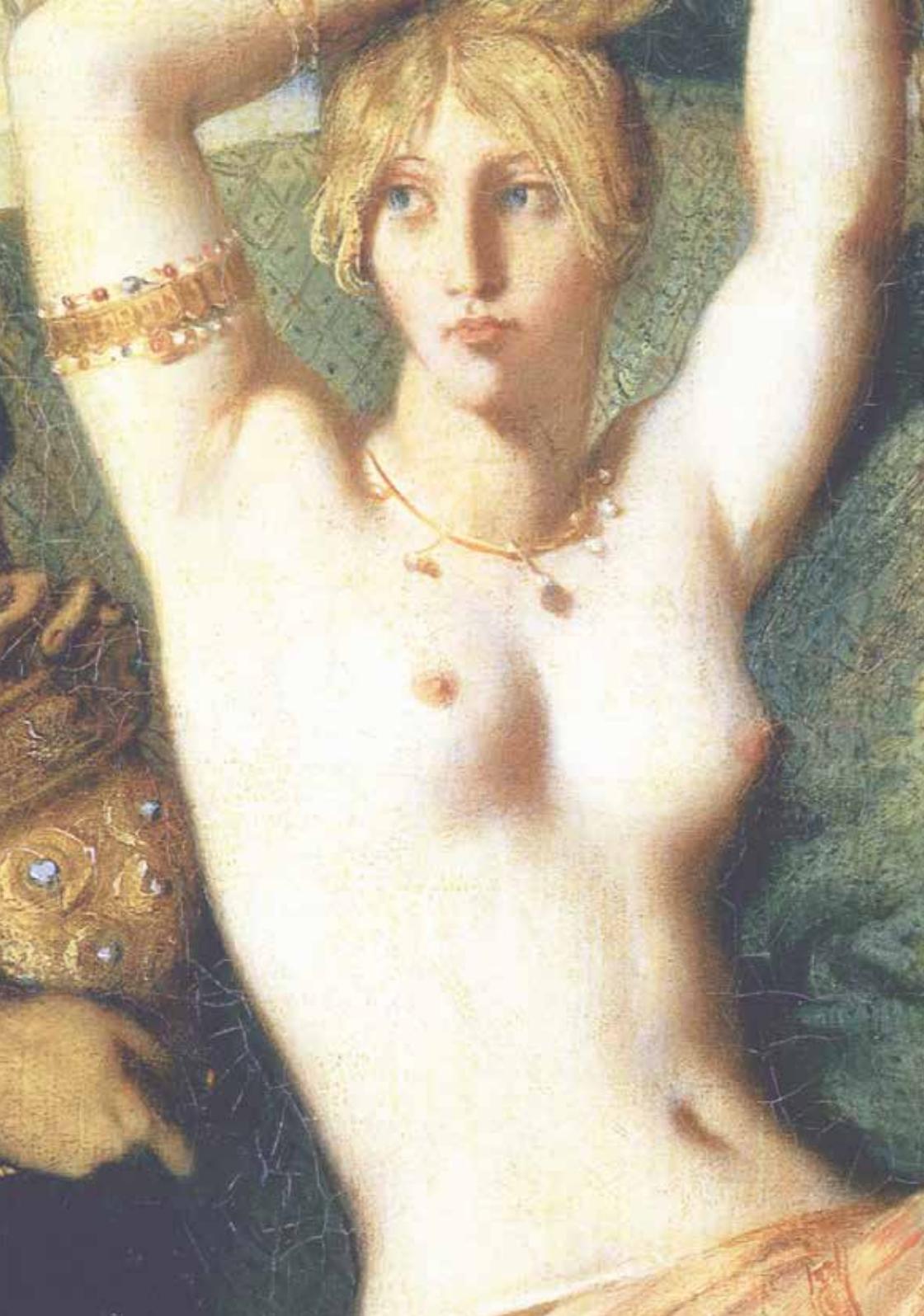


# METASTATIC BREAST CANCER



Member: EUROPA DONNA -  
The European Breast Cancer Coalition



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Gertrude Abela

President of Europa Donna Malta.



# METASTATIC BREAST CANCER

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**T**his brochure came about because a diagnosis of metastasis\* leaves you in a state of deep distress, regardless of whether it is a recurrence of a previous cancer or an initial diagnosis. You understand that it's something serious, but what does it actually mean?

We live in a world of over-information, the drawback being that we hear and read a bit of "everything and anything", and it can sometimes be difficult to find our way around this vast amount of information, much of which is contradictory.

This brochure is intended as a roundup of all this information; it is obviously not exhaustive, since research is ongoing and new advances in treatment are being made every day. It is a joint and multidisciplinary reflection on what a diagnosis of metastatic breast cancer really means. We have taken on the challenge of sharing and passing on information to you, to provide you with the means to be able to take an active part in the treatment process.

Why do we have this aim? No doubt because metastasis turns cancer into a chronic disease, and this process has an inevitable impact on life, with the feeling of insecurity that it brings with it, forcing us to face the unacceptable, with the threat of death looming on the horizon. Uncertainty takes over our thoughts, time becomes an issue of prime importance. How can we regain control over this time that already seems to have been taken away from us?

We have to assimilate the shock that this term "metastasis" produces in us as we undergo various tests, accept the suggested treatments and, above all, deal with the side effects that may attack our feeling of

physical well-being. Not to mention the way our mind starts racing, the realisation of our own mortality, all those treatments that seem so harsh and the endless round of medical terms.

Sometimes it may all be too much for us, but eventually we have to get used to it. Can we really deny such a deeply distressing reality, even though this may be an effective form of mental self-defence? We know, of course, but temporarily pushing the threat to one side can perhaps offer us some respite in order to accept and to find within ourselves the resources we need to face up to this reality.

Other reactions are also possible, ranging from anger to depression and then resignation. They are all valid reactions, they are all healthy and they are all different because the psychological experience of women with metastatic breast cancer is highly subjective; each experience is individual, unique and specific to that woman.

What should be indispensable, on the other hand, is a non-abandonment agreement that every sick person has the right to expect and to hope for. That's to say, to be listened to and looked after by their carers and their families. It goes without saying that talking about the seriousness of your disease, and even more your death, can scare the people around you, including medical staff, and so you may come up against resistance or an attitude of denial. This doesn't imply at all that you will be left alone to face this reality. Don't forget that your medical team is at hand, ready to help you. Don't be afraid or embarrassed to talk about what you need or what is worrying you, especially with regard to your sex life, which can play such an important part in your quality of life.

The team must also be there to understand your low spirits and your disappointment, your anger and your anxieties but, with the right tools, they will be at your side in your uphill battle to regain your self-esteem, which has taken a real beating with this new attack, this treachery. It's up to each person to find the way to do this, according to your personality! All things considered, what we all hope for when faced with such a reality is of course to get better. But unfortunately, that's the only thing that the doctors can't promise us. What they can offer, though, are the best possible treatments to fight the disease and to live life in a way which will allow moments of pleasure, because the awareness that you are going to die can trigger some unexpected defences.

Never mourn before the time, because knowing that your life has a time-limit can turn out to be an investment and can bring about a phenomenal will to live.



# What is cancer?

*Cancer is not a single disease but many different diseases with the same name. It is difficult to accept this fact from the start, because everyone associates cancer with death and believes that the outcome is always the same, regardless of what you do. However, some cancers can be cured, while others do unfortunately have a fatal outcome, regardless of treatment, and without anyone being able to predict when.*

## Features common to all cancers

### UNCONTROLLED CELL GROWTH

One feature is common to all cancers: the initial uncontrolled growth of a cell. The cell is the basic unit of our body. A number of cells together form tissue, which may be bony, muscular, connective, glandular, epithelial, and so on... which make up our organs (the lungs, the colon, the breasts, etc.). Our cells develop, grow and die every day. They are controlled by a number of different factors (such as genes, hormones, growth factors and enzymes) which are all involved in this balance. They are renewed regularly: a “mother” cell divides into two “daughter” cells, and this makes up the cell cycle. Each kind of tissue has its own rate of growth, with some tissues renewing at a faster rate than others. This division ensures that cell reproduction is identical, meaning that the cells keep their roles and their specific features, in order to ensure the function of each tissue and each organ. The body recognises abnormal cells and destroys them. So an irregular daughter cell will be destroyed by various mechanisms. One of these mechanisms is known as apoptosis, or programmed cell death.

## ONCOGENES AND ANTI-ONCOGENES

So cancer is associated with an abnormal proliferation of cells where the body's defence mechanisms are no longer working. Under the action of certain stimuli, some genes will cause unlimited tissue growth. These genes are known as oncogenes\*.

The body also has anti-oncogenes which prevent cancers from developing by permanently suppressing the factors that are likely to trigger them. These tumour suppressor genes can also mutate and cancer is usually caused by an imbalance between oncogenes and anti-oncogenes. Cancer is therefore a disease where the genes are sick, though the majority of cancers are not genetic in the hereditary meaning of the word.

The result is often that cancerous cells have an accelerated cell cycle with a fast doubling time. A cancerous mother cell will make two cancerous daughter cells, and so on. This proliferation is continuous, since the cells have become immortal. From the biological viewpoint, however, cancer is not a disease that occurs suddenly. From the moment that the first cell becomes abnormal, it takes between three to seven years for a tumour measuring one cubic centimetre to form.



# What is Metastasis?

## DEFINITION OF METASTATIC DISEASE

Cancer cells can break through the basement membrane\*, often due to the action of enzymes which partly destroy it and so allow them to spread beyond the original tissue. This spread is helped by their capacity to separate from each other, which is far greater than that of normal cells.

Cancers are also able to make their own blood vessels to provide them with their energy input. This is known as angiogenesis\* or neoangiogenesis\*. Cancers are generally rich in blood vessels.

Cancer cells spread through the body using the lymphatic system or the bloodstream. Metastases are formed by this distant spread, by distant reproduction in another organ of a tumour that is the daughter of the original tumour. These cells must then be able to attach themselves to the wall of a blood vessel, then proliferate, then break through the wall of the vessel to invade the surrounding tissue.

The metastasis from the tumour then has to develop a new vascular supply to feed on and grow, often by using the growth factors of the local tissue.

A good number of cancer cells are destroyed by the body's natural defences, the cells of the immune system, but some manage to slip through the net. These are generally the most resistant and the most aggressive. Then the cancer cells spread to different organs. Metastases can emerge at various stages of the disease. It is uncommon to discover it straightaway, at the same time as the initial tumour. They can sometimes show up several months or years after the occurrence of a cancer. It is thought that cancer cells can "sleep" in an organ, only to wake up at any time due to the action of factors that are

largely unclear. The cancer can therefore spread far from the initial tumour very early on and produce micro-metastases that can't be detected by current methods.

In their development, these metastases turn the body's metabolism\* to their advantage and obstruct the normal working of the organ where they are located. In the case of liver metastases, the liver can no longer cleanse the body of waste; if a lung is affected, it no longer carries out the exchanges between blood and air, and so on. It is this ability to alter certain vital functions that can lead to the death of the affected person.

## Metastasis: What are the warning signs and what tests can be done?

*Breast cancer is a cancer where the cancer cells can attach themselves to any tissue in the body. The bones are the most common site for metastases, but other sites include the skin, the lymph nodes, the lungs and the pleura, the liver and the brain.*

- MONITORING** is an essential tool for discovering metastases. A diagnosis of metastatic breast cancer will be based on:
- Recently developed and persistent clinical signs expressed by the patient: "I've got a pain in my back, a lump has appeared, I've got a cough, I've got a headache..."
  - During a routine medical test: an abnormal lymph node, an enlarged liver, a lung which isn't functioning as well as the other one... these are all signs that will alert the doctor.
  - An abnormal laboratory test result.

*\*see glossary on pages 34-36*



## WHICH TESTS?

Once the diagnosis has been suggested, it must then be backed up: firstly, a chest, abdominal or bone scan. If these tests are normal, then a CT or PET scan\* might be carried out. Tumour markers\* will be measured: CA 15/3 and perhaps also CEA, as very high levels of these are indicative of metastases. An MRI\* may also be useful to detect bone or cerebral lesions. It is becoming increasingly common to take a biopsy of the metastasis in order to analyse it and to know its characteristics (whether or not it is hormone sensitive\*, the presence of HER2\*) so as to have more targeted treatment.

## METASTASIS: A CHRONIC DISEASE?

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Various treatments can be used to control the development of metastasis and to slow down the process of it spreading throughout the body, but we can no longer speak about a cure in the true meaning of the word. Sooner or later the cancer will get another chance to show itself and each advance of the disease will require a new way of handling it. Metastatic breast cancer is a chronic disease that develops differently from one patient to another.

People often ask about life expectancy with metastatic cancer. The figures aren't pleasant to read or to hear. In medical jargon we speak about median survival time, which means the point at which half the specific population is still alive. For metastatic breast cancer, the median survival time is currently around 2 to 3 years. Some patients may still be alive over 10 years after the diagnosis of metastatic breast cancer; but this also means that some may die after just a few months.

# Treatments for Metastatic Disease

*Treatment is essentially based on chemotherapy, hormone therapy and targeted therapies. Radiotherapy and surgery are sometimes needed, as well as symptomatic treatment to control pain, improve quality of life and increase tolerance to treatments. These various therapies may be given alone, in combination or one after the other, depending on the characteristics of each tumour and previous treatments and are, of course, adapted to each person. These treatment strategies must be decided by a team, and also your opinion must be taken into consideration, knowing that it involves a whole series of treatments which will be effective for an amount of time that is more or less limited.*

## CHEMOTHERAPY

**ITS AIM: TO DESTROY TUMOUR CELLS.**

Monochemotherapy (a single drug) or polychemotherapy (a combination of drugs) can be used. The choice depends on the patient's conditions, the type of tumour and the likelihood of response to the proposed treatment. There are a number of different molecules and protocols to choose from. The choice is based on the statistical probability of effectiveness, while bearing in mind that at individual level effectiveness is always 100%: the treatment either works or it doesn't. This can only be known after two or three rounds of treatment: these drugs need time to take effect and shouldn't be changed too quickly.

*\*see glossary on pages 34-36*



## Possible outcomes:

- The metastases disappear completely: we can then speak about a complete response.
- They may reduce in size: we speak about a partial response if over 50%.
- They remain stable: chemotherapy blocks the proliferation of the tumour but doesn't reduce the size of the tumour.

Long-term stabilisation can sometimes be as satisfactory as a response that is complete but only lasts a short while, which is not always easy to understand.

There are many different chemotherapy drugs and combinations of drugs. The most common drugs used for metastatic disease are taxanes (docetaxel, paclitaxel), anthracyclines (such as doxorubicine, epirubicine, liposomal anthracycline), vinorelbine, gemcitabine and capecitabine. Some of these drugs can also be used in combination with targeted therapies. An effective and well supported protocol will be kept up for as long as possible and will only be changed if it becomes ineffective or if the disease advances. It will also be changed if the treatment is too toxic. Studies tend to show that treating patients “continuously” improves relapse-free survival and quality of life.

### MODES OF ADMINISTRATION: INTRAVENOUS OR ORAL

Most chemotherapies are given through a drip. Patients may be offered a central venous catheter\* connected to a subcutaneous infusion port. This is generally inserted under local anaesthetic. The rate of administration depends on the protocol used.

Some drugs may be administered orally, but they are still proper chemotherapy drugs. **It should be noted that if a chemotherapy drug is well tolerated, this doesn't mean that it is ineffective. There is no link between effectiveness and toxicity.**

\*see glossary on pages 34-36

## ADVERSE EFFECTS OF CHEMOTHERAPY

Chemotherapy attacks cancer cells but also attacks all the cells in the body that multiply rapidly. Healthy tissue repairs itself spontaneously while cancerous tissue has lost this ability to repair itself.

### Chemotherapy can cause:

- Interruption of the menstrual cycle in young women, and may even induce early menopause, with all the related symptoms.
- Nausea and vomiting. There are currently some very powerful drugs to prevent this. Most of the time patients don't vomit any more, but they may feel nauseous for several days after treatment.
- Irritation to the mouth (sores) and even ulcers. Preventive measures (mouthwash) can lessen the risk of this happening.
- Episodes of diarrhoea and constipation, the latter also being caused by the drugs prescribed to prevent vomiting.
- Hair loss (alopecia) and possible loss of pubic hair, eyelashes and eyebrows. A cold cap which is worn when chemotherapy is being given may reduce this, since the cold causes the constriction of the scalp vessels. This protection works in about half of cases, but it can also be hard to bear. A wig is usually worn when hair loss occurs.
- Fatigue: this is felt during and after the injections and may last several days. It can even continue for ten or so days after the treatment. It is most often caused by a drop in red blood cells and a state of anaemia. This can be corrected by erythropoietin, a product that stimulates the bone marrow, which is the source of these blood cells.
- Chemotherapy also causes a drop in the number of white blood cells which fight infections. If they get too low, a subcutaneous treatment to increase them (G-CSF or GM-CSF) may be offered, though this stimulation may cause bone pain. This is why the number of blood cells is checked before each chemotherapy session. A major drop in numbers is called



aplasia\*. If the patient has a temperature, this is known as febrile aplasia, which must be treated with a course of antibiotics, and hospitalisation may also be required.

### **Some drugs (such as taxanes) have distinctive adverse effects:**

- nail toxicity
- oedema (swelling) of the hands and feet
- skin rashes
- allergic reaction,
- nerve damage, which manifests as pins and needles (paresthaesia) and even a loss of hand and foot sensitivity
- hand-foot syndrome (redness of the palms of the hands and the soles of the feet, which may also be accompanied by extremely dry skin, even painful cracks). In this case, it's essential to keep the skin moisturised
- cardiac toxicity which, for some drugs, requires regular heart ultrasounds or cardiac scintigraphies to monitor the force with which the heart contracts.

There are many different side effects. Each woman reacts differently and it's up to the medical team to adjust and optimise the treatment.

# HORMONE THERAPY

*This is offered when the tumour is hormone-dependent. It's the treatment of choice for elderly women and patients with slow growing tumours. It's an active anti-hormonal treatment for patients with cancers that express oestrogen receptors.*

## PRE-MENOPAUSE

The ovaries secrete oestrogens. So Tamoxifen, an orally-administered drug, is prescribed to take the place of oestrogens on the hormone receptors. It inhibits the growth of tumour cells in the breast and in metastases.

Tamoxifen has a different mode of action depending on the tissues of the body: it's an antioestrogen for breast cancer cells but, paradoxically, it has an oestrogen-like action on normal bone (which is positive with regard to osteoporosis) and in the vagina (which encourages good vaginal secretion). This action is also good for the heart.

The adverse effects of Tamoxifen are basically hot flushes, possible bouts of depression and weight gain. Its oestrogen action slightly increases the risk of thrombosis and may cause thickening of the lining of the uterus (endometrium) and even endometrial cancer.

Sometimes LHRH analogues are used to induce a reversible artificial menopause by blocking the production of oestrogen by the ovaries, which causes a sudden onset menopause with the associated symptoms. They are administered by subcutaneous injection every 1 to 3 months. Studies have shown greater effectiveness when LHRH analogues are used in combination with Tamoxifen.



## POST-MENOPAUSE

Tamoxifen can also be used after the menopause. However, aromatase inhibitors (anastrozole, letrozole, exemestane) are more commonly used. Aromatase is an enzyme that allows the conversion of androgens\* into oestrogens. In postmenopausal women, androgens are produced by the suprarenal glands and the ovaries. Aromatase inhibitors prevent this conversion even in tumours and metastases. These drugs are also taken orally. The most common adverse effects are joint pain (arthralgia) and muscle pain (myalgia). There is also a significant risk of osteoporosis and fractures. Patients may sometimes complain of diarrhoea and vaginal dryness and a loss of libido.

New on the market is a drug called fulvestrant, a pure antioestrogen which, unlike Tamoxifen, has no oestrogen action on the bones and the uterus. It's effective when Tamoxifen can no longer control tumour growth. It's administered as a once-monthly intramuscular injection. Other hormone therapies have been used in the past: high-dose oestrogens and progestogens as well as androgens. They are much less commonly prescribed nowadays, however, due to their adverse effects.

## HORMONE THERAPY IN PRACTICE

Hormone therapies are generally used one after the other. An active hormone therapy may become ineffective after some time, so another drug may need to be used. A series of hormone therapies may be used before going on to chemotherapy. Hormone therapy can also be used as a maintenance treatment, after chemotherapy or alternating between chemotherapy and hormone therapy if required. Lastly, new combinations, particularly with targeted therapies, are currently being studied.

\*see glossary on pages 34-36

# TARGETED THERAPIES

*While targeted therapies show great promise for breast cancer treatment, there are a number of question marks for the main people involved, that is, the patients.*

## What is meant by targeted therapy?

*Any treatment whose mechanism of action is known and whose target is known and identified is, in theory, a “targeted therapy”. This includes some chemotherapies which act on dividing cells, whether these are cancerous or not.*

*In recent years, significant advances made in biology have allowed us to find the most characteristic targets of cancers in general (non-specific targets) or particular cancers such as breast cancer (specific targets). Some kinds of cancer are increasingly being defined by the existence of a specific therapeutic target.*

### NON-SPECIFIC TARGETS

With regard to general cancer targets, you can imagine the interest in suppressing the main sources of the tumour’s energy, that is, the supply of oxygen by vascularisation, and also the energy supply, by acting on the cell metabolism. This is how anti-angiogenic drugs are currently being used in practice and why drugs that work on insulin receptors are being developed. This “targeting” is no less general. It would also seem sensible to prevent cells which have a tendency to metastasise, or which have already metastasised, from developing in the organ in which they are found. Some drugs that target the bones prevent the progression of bone metastases (bisphosphonates\* and RANK Ligand inhibitors\*).

*\*see glossary on pages 34-36*



Other drugs currently being developed aim to prevent cancer cells from lodging in certain organs.

## SPECIFIC TARGETS

These are targets that are basically present on or inside cancer cells, which gives them an “advantage” over normal cells.

These cells try to survive in some way, either by capturing all the sources of energy that enable them to proliferate, or by looking for a way to become “immortal” in some way.

These targets are very often proteins which have the function of receptors\*, mostly growth factor receptors. In recent years it has been shown that these different receptors can interact with each other by forming communication networks that could be compared to roads. Like all road networks, there are important checkpoints at the intersections. In cells, these crossroads are ensured by other proteins which have been identified as new targets.

Moreover, knowledge of certain hereditary forms of cancer has allowed the identification of specific abnormalities that have themselves become new targets. This is the case of breast cancers associated with the BRCA1\* and BRCA2\* mutations, proteins which are involved in the repair of DNA\*. The major difference is, therefore, that instead of using the same treatments for everyone, specific targets allow us to select the patients who will benefit from them.

Specific targets are to be found on the tumour while the other targets are mostly found around the cancer cells.

## Specific targeted therapies currently used in the treatment of metastatic breast cancer

*These can be divided into two large families: antihormonal targeted therapies and antiHER2 targeted therapies.*

**ANTIHORMONAL TARGETED THERAPIES** prevent cancer cells that have oestrogen receptors from being stimulated by the body's oestrogen, either by preventing them from establishing themselves (competitive inhibition by Tamoxifen or fulvestrant), or by hindering their production (aromatase inhibitors).

Other approaches are currently being validated, such as combining chemotherapy with an oestrogen hormone for targeted delivery of the chemotherapy to the site of the cancer cells with these receptors. Almost 70% of metastatic breast cancers have oestrogen receptors.

**ANTI-HER2 TARGETED THERAPIES** target the HER2 receptor which is present in significant quantities in around 20% of metastatic cancers. Specific antibodies (trastuzumab) or small molecules (lapatinib, neratinib) can block its action. New antibodies can be used to block this receptor, which can combine with other receptors (pertuzumab) in a different way. The combination of an antibody with chemotherapy enables the targeted delivery of the chemotherapy into these cells (TDM1) and it seems increasingly evident that the use of two different therapies targeting this receptor is more effective than a single therapy.

When stimulated, the oestrogen pathways and the HER2 pathway trigger a whole series of cascade reactions in the cancer cell, but these pathways cross and new treatments are targeting proteins in these junctions such as the mTOR\*

\*see glossary on pages 34-36



protein (RAD001). The addition of mTOR targeted therapy to antiHER2 and anti-oestrogen therapies seems to hold promise for the future.

Lastly, some breast cancers do not have hormone receptors or HER2 receptors. These cancers, known as “triple negative” are more often found in hereditary and familial forms of cancer. Some new treatments that target certain DNA repair proteins show significant promise, though an exact target has still not been clearly identified.

## Are targeted therapies less toxic?

**YES AND NO** Specific targeted therapies are generally less toxic as their targets are mainly present in the cancer cells. These targets may also be found in normal cells, which is the reason for a certain amount of toxicity, such as the presence of HER2 receptors in heart cells or oestrogen receptors in bone and joint cells.

Nevertheless, specific targeted therapies can improve the “therapeutic index”, that is, they can significantly increase the positive effects (control of the disease) as against the negative (or toxic) effects.

## Are targeted therapies given orally or by means of injection?

**BOTH WAYS ARE USED** Antibodies\* are currently administered intravenously and some are being developed for subcutaneous administration. The injection is administered every three to four weeks. Other therapies, generally made up of smaller molecules, are often taken orally.

## Is treatment by targeted therapies shorter?

**NO,** in fact the opposite is often true, in the hope of being able to cure patients by means of these targeted therapies. The more the target is specific to the disease, the more the treatment or treatments targeting it will probably be used for a long period.

\*see glossary on pages 34-36



## Can targeted therapies be used in combination?

**YES,** it seems that some targeted therapies are even more active when taken in combination than separately. Indeed, if we go back to the image of a road junction, the more we block the roads (rather than blocking a crossroads), the less the cell will be able to send survival signals.

## Can targeted therapies be used without chemotherapy?

**YES,** but often it is the combination of a targeted therapy that makes the cell fragile, making it sensitive to chemotherapy which will destroy it more easily and give better results. We've also seen that some targeted therapies are directly combined with chemotherapies (the two being attached to each other) to deliver the chemotherapy specifically to the cell. This is known as "vector targeted" chemotherapy.

# SURGERY

*Surgery, like radiotherapy, is basically a local treatment to remove the tumour. It is most effective when the cancer is localised and/or when there is a single metastasis. In the event of several metastases, surgery may sometimes be necessary to prevent and treat serious complications of the disease.*

## In the breast

The initial tumour can be removed even when the cancer is metastatic at diagnosis. Surgery will be a lumpectomy or a mastectomy if necessary, to remove a tumour mass which may otherwise continue to send cancer cells elsewhere. Recent studies tend to show that this can improve survival in the metastatic setting. Moreover, women are often relieved to get rid of this tumour that they can feel under their fingers. These treatments are always discussed by a multidisciplinary team while taking the patient's opinion into consideration. Surgery may also be an option when there is a recurrence in the thoracic wall, sometimes even several years after removal of the breast: this is a rare situation which requires surgery. Surgery can be part of a tumour-reduction strategy in combination with chemotherapy, hormone therapy and targeted therapies.



## Metastases

Some metastases, such as in the liver or the lungs, can be removed by surgery after medical treatments have destroyed most of the metastases, or when there is a single metastasis which is accessible to surgery. This is valid for metastases on diagnosis and for those occurring years after the diagnosis of the initial tumour.

In these cases it is thought that the metastatic disease must be controlled as much as possible by medical treatments in order to get the maximum benefit from surgery. Suggesting surgery would be of no benefit to patients if the disease is progressing or if there are too many metastatic spots.

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## The specific case of bone metastases

### **METASTASES ON THE LONG BONES OF THE ARMS AND LEGS**

risk causing a painful and debilitating fracture, such as a femoral neck fracture. Surgery could be suggested before the fracture takes place (intramedullary nailing, implant).

**SOME VERTEBRAL METASTASES,** not threatening for the nervous system but very painful, could benefit from a bone cement injection (vertebroplasty) in the affected vertebra or vertebrae.

Vertebral metastatic disease that compresses the bone marrow or a nerve root can cause paralysis. Immediate surgery is therefore required in order to relieve the nervous system and stabilise the spine by means of a metal bracket which can be combined with vertebroplasty.

In all these cases, the operation is followed by radiotherapy (at least 10 days after surgery) in order to work on the remaining cancer cells.

In the brain, an operation is carried out as first-line treatment if there is a single lesion which is accessible to surgery.

# RADIOTHERAPY

*Radiotherapy is a local treatment that works directly on the metastases and which is used in conjunction with other surgical and medical treatments to fight the tumour, relieve pain and improve the patient's quality of life.*

*This technique, widely used in cancer treatment, uses radiation to gradually destroy the cancer cells by preventing them from multiplying while at the same time saving as much as possible of the adjacent healthy tissue.*

## The treatment of bone metastases

**In this case, the aims of radiotherapy are as follows:**

**TO RELIEVE PAIN** : the effect is rapid and constant, even if sometimes there may be a further outbreak of pain after the first sessions. The patient will experience rapid relief, improved mobility and a better quality of life.

The number of sessions and the radiation doses will depend on the intensity of the pain, its functional impact on daily life and the patient's mobility and general state.

**TO REDUCE THE RISK OF FRACTURES** by helping the bone reconstruction of areas that have been decalcified by the metastases; this bone consolidation is obtained in the 3 to 6 months following radiotherapy. Bisphosphonates are currently often used in conjunction with radiotherapy in order to increase this effect.



## WITH VERTEBRAL METASTASES, TO PREVENT VERTEBRAL COMPRESSION,

a source of medullary and neurological compressions. The spinal column is in fact a common site for metastases. There is a significant risk of neurological complications: pain on the nerve root pathways, medullary compression, problems in urinating or defecating, even paralysis of the arms or legs.

Treatment will vary depending on whether there is a single spot or multiple locations, whether cervical, dorsal or lumbar areas are affected, and especially if the nerve roots are affected or in the event of medullary compression.

In this case, primary surgery is indicated if the patient's general state of health allows it, to free the medullary canal quickly to give more or less full neurological recovery. Radiotherapy will then be used to consolidate this.

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Radiotherapy can therefore be used as treatment for painful bone metastasis in an area that has not previously been irradiated or where irradiation was not at the maximum dose, since there are maximum doses allowed for each organ.

The radiologist, together with the radiotherapist and using electronic measurement tools, calculates the radiation times and the doses to be given on the metastatic target, limiting radiation of the neighbouring healthy tissue. Medical supervision is necessary to ensure that the treatment is effective and well tolerated.

## The treatment of brain metastases

Radiotherapy can relieve pain, neurological symptoms such as balance disorders, headaches and speech disorders, thus improving the patient's quality of life. It often means a more or less full irradiation of the brain by additional doses on the metastasis or metastases.

Since radiation treatment may often cause early cerebral oedema\*, cortisone treatment is usually prescribed along with radiotherapy in order to prevent this oedema, which can be

\*see glossary on pages 34-36

a source of headaches, nausea and even vomiting. Memory problems may appear even some time after treatment. Nevertheless, if only an isolated part of the brain is affected, some localised radiotherapy techniques can be used which avoid the secondary effects of total brain irradiation.

## What are the side effects?

### **It depends on the area irradiated.**

While these are relatively rare and minimal with irradiation of the long bones of the arms and legs and mainly affect the skin (cutaneous erythema, radiodermatitis), they can be much more significant when other parts of the body are irradiated:

- Chest: oesophageal disorders – problems and pain in swallowing, even late development of stricture\* - and lung disorders: coughing and shortness of breath.
- Abdomen and pelvis: mainly diarrhoea and/or pain, a burning sensation while urinating or a frequent need to urinate.
- Spinal column: it is rare for the spinal cord to be affected by radiation. However, it may cause shooting pains, sensitivity disorders, motor disorders and even paralysis.
- Hair loss is very often observed at the end of treatment, with regrowth starting around 3 months after the end of radiation.



# WHAT IS A CLINICAL TRIAL?

As you've seen, managing metastatic cancer is a major challenge with regard not only to results and effectiveness but also to strategy, given the complexity of the choice of treatments.

In order to better define the treatment strategies, doctors have to evaluate these strategies scientifically. This evaluation includes carrying out clinical trials during which a traditional strategy is compared with a new strategy (which may be a new treatment, a new combination or a new method of administration) so that, if the new strategy is better, it can be incorporated into everyday practice as soon as possible.

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# AND YOUR QUALITY OF LIFE?

Learning that your breast cancer has spread is a devastating blow. It means that you are going to have to start again with all the treatments that it took you so long to get over and which you remember only too well. You may well also have less confidence in your healthcare team, and you may want to try some alternative or complementary treatments. This type of therapy may help you, but it must not interfere with the action of validated medicines because, at this point, the time window to start appropriate treatment is often very limited.

Your quality of life is at the forefront of your concerns, because you're well aware of the trauma that you're going to have to pass through and you've understood that your lifetime may be cut short. Everything must therefore be done to limit your suffering, whether this is due to the disease itself or the side effects of the treatments. There are many drugs available that

can make you more comfortable and help you cope better. You should be aware that doctors have never before had such an effective and impressive arsenal of treatments at their disposal as they have today. Moreover, recent statistics show a significant improvement in the survival rates of people with metastatic breast cancer. A doctor-patient relationship based on mutual trust is thus an essential condition in order to live this disease in the best possible way. It is becoming more and more a chronic disease, with longer remission times, and in which suffering is increasingly better controlled.

### SUFFERING AND SUPPORTIVE CARE

Pain management is essential, and must be a priority. We know that breast cancer can cause pain, especially in the bones, which you may particularly dread. Doctors have come to understand that pain is “subjective”, i.e., that only the person feeling it can talk about it, and that it is “individual”, i.e., that it “is what the patient says it is”. Consequently, any unpleasant symptoms can cause what is known as “psychogenic” pain which can make them worse. Fortunately, the use of active treatments based on morphine has become more common in recent years. When used properly, these medications can lead to significant improvements in pain control. If your doctor feels that the pain relief achieved is not sufficient, he/she may refer you to a pain management expert, who will have other methods and techniques available to provide you with better pain control. Before pain, however, the first complaint you’ll have with metastatic breast cancer is fatigue. Often neglected, it is nevertheless a trigger that can make you feel unwell. Any fatigue that is felt must be understood, since it’s usually caused by a number of different factors, and carefully analysed in order to prevent possible complications. This is why, when you feel extreme tiredness (fatigue), you should tell your doctor, so that he/she will try to find the source of the fatigue.



Around a quarter of you will pass through a period of depression or feel very anxious. This may aggravate your way of feeling pain and suffering and will be closely linked to it. Conversely, some things that you feel, such as chest pains or breathing difficulties, may lead to emotional decompensation. With this in mind, if psychotropic drugs can help you, it would seem obvious that a psychotherapeutic approach would be appropriate for you.

Eating disorders are another symptom that can make you feel worse. Nutrition problems are quite frequent with cancer. They may lead to weight loss or, conversely, weight gain, which may be caused by certain chemotherapies. Fortunately, dietary research has made great progress and nutritionists are applying their discoveries in the field of oncology. You shouldn't hesitate to go to a nutritionist if you experience problems.

The recent awareness of these phenomena, and their evaluation, has led to a new attitude to this type of care which is now known as supportive care.

Too many patients won't get better, even though they can live for a long time with the disease. A number of molecules and innovative techniques are nevertheless being developed which can help you with the various ordeals that you're going through. Whether this is by means of various psychotherapeutic methods, new manual kinesitherapy methods, such as biofeedback\* or transcutaneous electrical nerve stimulation (TENS), acupuncture or even current research on relieving pain through hypnosis or sophrology (mind/body exercises), all these processes have the same aim: to help you overcome feeling unwell as a consequence of this disease.

# YOU'VE HEARD ABOUT "THE WILL TO LIVE": WHAT DO YOU THINK?

"The cancer, my cancer, has woken up; it was sleeping in the innermost depths of my body, of my life, and just like an Icelandic volcano, it's come to life again. I can't trust my body any more, it's betrayed me once again, and medicine has deceived me, Of course, I knew that cancer kind of takes us hostage", you think to yourself, "but the hope of escaping its clutches has kept me going to now... and now I've been taken back by force."

A disease without a beginning and without an end, but marked by varied and variable episodes, whether expected or unforeseen, giving the unpleasant impression that neither yourself nor your doctors are really in control of the situation. And yet everyone's giving their all! So, metastasis, when you've got us... it may be just the two of us... but it's also many others!

Today just like yesterday, it isn't a question of survival, but always of life. So, it's not about forgetting feelings and not sharing pleasures and desires, and even less about the ways of expressing them. Metastatic disease must not extinguish the will to live.

Talking about love without making love can help you overcome pain or discomfort, a temporary time where caress rhymes with tenderness and femininity goes with voluptuousness. If some moments, some positions, make you feel more fragile and above all more anxious, don't hesitate to say so and to experiment in order to find others that may be better. Forget the scars, the blemishes, the losses, and make peace with these signatures of the disease instead. Above all, don't hesitate to express your fears: you'll find them less impossible

*\*see glossary on pages 34-36*



to overcome if you put them into words. They will above all allow your partner to understand the situation without feeling rejected, or even undesirable, which will in turn reinforce the same feeling in you, and a vicious circle will soon have been created.

Let's instead try to replace this with the famous virtuous circle, which is very fashionable nowadays, but where virtue is not abstinence but the discovery or the rediscovery of a loving relationship. And if the heart and the head have to unite with the body to support it, the romantic encounter will not lose any of its value, it will give reassurance but also happiness: taking and giving love and pleasure, that's living life to the full, relegating the disease to the background.

Never forget that, metastasis or not, you haven't lost your place in society, or your passport to the world of friends and romance. You are still worthy of being loved, of desiring and being desired, just like before. Just yesterday, everything seemed to be resolved, simple and clear; you felt that calm had been restored, but now today the storm has risen up again: so you have to get down to work again, gather your forces against this new attack and rebuild your confidence in yourself, in your body.

A new medical or surgical attack as well, with its impact on any decisions you'll have to make. As you know, an ovariectomy or hysterectomy (removal of the ovaries or the uterus) makes childbearing impossible, but on the other hand it avoids the need for contraception. The same goes for certain non-surgical treatments but, depending on the treatments and your periods, some form of contraception may still be necessary. The coil remains the most logical choice. In any case, don't hesitate to speak up with your questions: as the saying goes, there's no such thing as a stupid question, even if the answer isn't always the one you expected...

"Why me, why now?"; anxiety and loss of confidence can make you more fragile in your relations with those around you. Don't feel that you have to hide your moments of "low tide",



or your tears. There's no shame in it, you have the right, just as you have the right to seek out the shoulder of a friend or a lover to restore your balance.

So there's no shame if this battle to rediscover yourself is fraught with moments of discouragement, or even anger: it's perfectly understandable, and perhaps it's even necessary! Anger, the desire to live, is an excellent driving force, perhaps the best one to prove to yourself, to others and to "the other" that, as Fellini wrote, "There is no end. There is no beginning. There is only the infinite passion of life..."



## AND YOUR LOVED ONES?

The anxiety aroused by the word “metastasis” is magnified by the thought of having to tell your nearest and dearest. Saying it out loud, naming it, makes it true. It means hearing it again, which you dread, and which often makes you put off telling them, as if to absorb it better yourself or perhaps even to push it away.

How should you tell them? What words should you use so as not to upset them too much? How can you play the situation down? And what about the children? What words can you use to suit their age?

So many questions that jostle with each other and often prevent you from putting your feelings into words. Your thoughts seem to be “frozen” and you may need some time for them to “thaw out” so that the truth can be put into words. Yet at other times, you may want to throw the truth into the face of your loved ones as violently as it was when you heard it, almost as a form of “revenge”, as proof of your anger and of the injustice of being struck by this migration of cancer cells. The loss of control of your body may lead to a loss of control of yourself... at least for a while. Once again, all these reactions are normal.

Because you’ve understood only too well: there’s no miracle solution, no softer words, no right time. Everyone has to take control of this reality, absorb it, make it their own in their own time, which is different for each of us, whether one is a patient, a loved one, an adult, a child...

The harmful effects of silence and of things left unsaid are well proven. Children in particular need this “truth with gentle words”. Your illness is a part of their lives, and they have to know about it so that their often very vivid imaginations don’t make them even more upset. They can understand a lot if at the same time they are immersed in love and kindness. There

are no good or better words, just as there are no bad words: there's just a reality to share.

The same goes for our parents and older relatives. In our desire to protect them, we often keep them away from what is going on. But they too can understand this cruel truth, in their own time and at their own pace. Imagine how betrayed they would feel if they learnt the truth from someone else! This is true for anyone, whether they are 6 or 75 years old! Trust in their ability to cope, even to support you and help you. Some trials and tribulations can help us to mature: that goes for both you and your loved ones.

And that's how life can go on, with the support of treatments! These help us in our attempt to regain control over these cells that have gone crazy, a battalion of soldiers to repulse the enemy, or at least to keep it in check if it can't be beaten.

They provide a framework in which we can think to the future and can also calm our fears and leave room for hope, for life and its rights, its joys, its desires, its plans.

These treatments enable you, you and your loved ones, to live and to continue along your journey despite this new medical reality. The "thaw" leaves room for the possible, for the creation of a life that is different, but still satisfying. The desire for life is ever present and will support you and your loved ones through these trials.

This brochure may help you to understand, to question and to exchange views with your loved ones as well as with the teams who are going to be with you on your journey.



# GLOSSARY

**ANGIOGENESIS:** process of growth of new blood vessels (new vascularisation) from pre-existing vessels. Angiogenesis is particularly involved in the growth of malignant tumours and the development of metastases.

**ANTIBODIES:** complex protein used by the immune system to detect and neutralise specific pathogenic agents. Antibodies are secreted by cells derived from B lymphocytes: plasma cells.

**APLASIA:** atrophy of a tissue or an organ.

**BASEMENT MEMBRANE:** an impermeable barrier on which epitheliums develop and which separates them from the underlying connective tissue. It provides a significant physiological barrier, particularly in the area of tumour pathology.

**BIO FEEDBACK:** kinesitherapy technique which uses measuring devices to regulate body functions by feedback.

**BISPHOSPHONATES:** drugs indicated in the treatment of osteoporosis and, in certain cases, bone metastases, by helping with bone remineralisation.

**CENTRAL VENOUS CATHETER:** a tube inserted in a large vein and left in place for a long time, even for life, to allow blood to be taken and to administer drips (implantable site). Also called a portacath.

**DNA:** this stands for deoxyribonucleic acid, which is found in chromosomes. It's a large molecule whose structure and chemical properties store the hereditary information which determines an organism's development and function. This information is handed down from generation to generation (heredity).

**EMOTIONAL DECOMPENSATION:** emotional state characterised by a significant alteration of the conscience and the perception of reality.



**HER2 (Human Epidermal Growth Factor Receptor 2):** this is a transmembrane protein which promotes cell growth. In around 20% of women with breast cancer, there is a hereditary change in the HER2 gene which leads to increased production of the HER2 protein on the surface of the cancer cell. In this case we speak about HER2 positive breast cancer. It's a particularly aggressive form which is treated with targeted therapies.

**HORMONE RECEPTOR:** a molecule which recognises and binds to hormones in the blood, which some cancer cells have. Research into these receptors is carried out on a fragment of tumour tissue.

**HORMONE SENSITIVITY:** said of a tumour whose growth is stimulated by a specific hormone.

**METABOLISM:** this term describes all the molecular and energy processes which take place continuously in the cells of every living organism.

**METASTASIS:** the spread of a tumour to a secondary location. Its presence is a factor in the severity of the disease.

**MRI (Magnetic Resonance Imagery):** a radiology technique using the properties of radiofrequency (RF) waves in a magnetic field.

**mTOR PROTEIN:** an enzyme that regulates cell growth.

**MULTIFACTORIAL:** dependent on a number of different factors.

**MUTATION:** this term is used to describe an irreversible change in genetic and hereditary information.

**NEOANGIOGENESIS:** the formation of new blood vessels caused by the growth of a tumour.

**ONCOGENE:** Oncogenes are a category of genes whose expression favours the occurrence of cancers.

**PSYCHOTROPIC DRUG:** a substance which acts chemically on the central nervous system and causes psychological changes.



**RANK LIGAND INHIBITOR:** in certain cases of metastatic cancers, the cancer cells are located in the bone tissue. They release factors which stimulate the secretion of RANK Ligand. This molecule is known for its role in bone resorption that can generate complications such as pain, fractures or the need for surgery.

**STENOSIS:** an anatomical change which causes the narrowing of a structure (canal or blood vessel).

**TUMOUR MARKERS:** a tumour marker is a substance found in the blood which corresponds to the presence or development of a malignant tumour.

## EUROPA DONNA MALTA: who are we?

We are the Maltese branch of a European coalition against breast cancer, comprising 46 countries with the objectives set out on the following page.

Our main objectives are to offer support to women affected by breast cancer and their families, and to provide information to all women, not only those affected by breast cancer, because we think that a woman who is well-informed will look after herself better when she is ill and will be able to react better.

We are fighting against something that has become a real public health problem:  
Over 300 new cases of breast cancer are diagnosed in Malta every year.

## The 10 goals of EUROPA DONNA:

1. To promote the dissemination and exchange of factual, up-to-date information on breast cancer throughout Europe.
2. To promote breast awareness
3. To emphasise the need for appropriate screening and early detection
4. To campaign for the provision of optimum treatment
5. To ensure provision of quality supportive care throughout and after treatment
6. To advocate appropriate training for health professionals
7. To acknowledge good practice and promote its development
8. To demand regular quality assessment of medical equipment
9. To ensure that all women understand fully any proposed treatment options, including entry into clinical trials and their right to a second opinion
10. To promote the advancement of breast cancer research





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